Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder - Results from a Systematic Review with Network Meta-Analysis

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ABSTRACT

BACKGROUND: Sexual dysfunction (SD) is prevalent in patients with major depressive disorder (MDD) and is also associated with second-generation antidepressants (SGAD) which are commonly used to treat the condition. Evidence indicates underreporting of SD in efficacy studies. SD associated with antidepressant treatment is a serious side effect that may lead to early termination of treatment and worsening of quality of life. OBJECTIVES: To systematically assess the harms of SD associated with SGAD in adult patients with MDD by drug type. METHODS: We retrieved English-language abstracts from PubMed, EMBASE, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts from 1980 to October 2012 as well as from reference lists of pertinent review articles and grey literature searches. Two independent reviewers identified randomized controlled trials (RCTs) of at least six weeks' duration and observational studies with at least 1,000 participants. STUDY SELECTION: Reviewers abstracted data on study design, conduct, participants, interventions, outcomes and method of SD ascertainment, and rated risk of bias. A senior reviewer checked and confirmed extracted data and risk of bias ratings. ANALYSES: Random effects network meta-analysis using Bayesian methods for data from head-to-head trials and placebo-controlled comparisons; descriptive analyses calculating weighted mean rates from individual trials and observational studies. RESULTS/ SYNTHESIS: Data from sixty-three studies of low and moderate risk of bias (58 RCTs, five observational studies) with more than 26,000 patients treated with SGAD were included. Based on network meta-analyses of 66 pairwise comparisons from 37 RCTs, most comparisons showed a similar risk of sexual dysfunction among included SGAD. Credible intervals, however, were wide and included differences that would be considered clinically relevant. We observed three main patterns: Bupropion had a statistically significantly lower risk of sexual dysfunction than some other SGAD, and both escitalopram, and paroxetine showed a statistically significantly higher risk of sexual dysfunction than some other SGAD. We found reporting of harms related to sexual dysfunction inconsistent and insufficient in some trials. LIMITATIONS: Most trials were conducted in highly selected populations. Search was restricted to English-language only. CONCLUSION AND IMPLICATIONS: Because of the indirect nature of the comparisons, the often wide credible intervals, and the high variation in magnitude of

outcome, we rated the overall strength of evidence with respect to our findings low. The current degree of evidence does not allow a precise estimate of comparative risk of sexual dysfunction associated with a specific antidepressant. In the absence of such evidence, clinicians need to be aware of SD as a common adverse event and should discuss patients' preferences before initiating antidepressant therapy.

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide, affecting 15 percent of the population in high-income countries once in their lifetime [1]. Antidepressants were the most frequently dispensed prescription drugs in the United States (US) in 2011 accounting for $11 billion in sales and 264 million prescriptions filled [2]. Sexual dysfunction, which can involve any or all phases of the sexual response cycle (i.e., libido, arousal, orgasm and ejaculation), is associated with both the condition and the treatments used, can affect up to 50 percent of untreated depressed patients [3, 4]. Particularly when treated with second-generation antidepressants (SGAD), depressed patients may experience antidepressant-induced sexual dysfunction [5].

Treatment-emergent sexual dysfunction is a frequent but often under-reported serious adverse event associated with the use of SGAD. According to the U.S. Food and Drug Administration (FDA), all adverse events resulting in a substantial disruption of a person's ability to conduct normal life functions can be considered serious adverse events [6]. Onset or worsening of sexual dysfunction as an adverse event associated with antidepressant use can result in premature discontinuation of antidepressant treatment, relapse of depression, and worsened health outcomes and quality of life [7-9].

Rates of treatment-emergent sexual dysfunction in depressed patients from randomized clinical trials range from 15 to 80 percent [10, 11]. Using data from a cross-sectional study in Europe, study authors estimated the prevalence of treatment-emergent sexual dysfunction in depressed patients prescribed either a selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitors to be between 37.1 percent and 61.5 percent [12]. Evidence indicates underreporting of sexual dysfunction in efficacy studies, particularly when no targeted or structured method is used to obtain information on sexual functioning, both at baseline and throughout drug treatment [13]. In a prospective observational study, investigators observed a considerably lower incidence of antidepressant-associated sexual dysfunction when sexual dysfunction was determined by spontaneous reports of study participants alone compared to using a validated sexual function-specific instrument: nearly 80 percent of those with treatment-emergent sexual dysfunction would have gone undiagnosed if only reported spontaneously [14].

A few systematic reviews addressed the issue of sexual dysfunction associated with SGAD in patients with MDD [10, 15-19]. With the exception of an updated meta-analysis by Gartlehner et al. [11], which also included data from observational studies, previous systematic reviews focused on efficacy trials. This study aims to systematically review

and assess the comparative harms of sexual dysfunction in MDD patients treated with SGAD using data from both clinical trials and observational studies.

2. Methods

This systematic review updates part of a larger comparative effectiveness review on SGAD funded by and conducted for the U.S. Agency for Healthcare Research and Quality (AHRQ) [19].

2.1. Data Sources and Study Selection

We searched PubMed, EMBASE, PsycINFO, the Cochrane Library, and International Pharmaceutical Abstracts from 1980 to October, 2012. We used Medical Subject Headings as search terms when available or key words when appropriate. We combined terms for MDD with a list of 13 specific SGAD (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine) and their specific trade names. We limited the electronic search to "adult 19+ years," "human," and "English language." We used semi-automated manual searches of reference lists of pertinent review articles and letters to the editor employing the Scopus™ citation database (www.scopus.com) [20]. The Scientific Resource Center (SRC) searched the following sources for potentially relevant unpublished literature: the U.S. FDA website, Health Canada, Authorized Medicines for the European Union, ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials, Conference Papers Index, National Institutes of Health RePORTER, HSRProj, Hayes, Inc. Health Technology Assessment, and the New York Academy of Medicine's Grey Literature Index. The SRC also asked pharmaceutical manufacturers to submit dossiers on completed research for each drug included in this review. We received dossiers from two firms (Astra Zeneca, London, United Kingdom [UK] and Warner Chilcott, Dublin, Ireland).

Two investigators independently reviewed abstracts and full text articles (each done by two out of the authors: UR, GG, LCM, AG, BN, RAH, MVN, LL, BNG). We excluded studies available in abstract form only. We developed eligibility criteria with respect to study design, duration, patient population, interventions, and outcomes to assess sexual dysfunction as harms associated with SGAD or as treatment-emergent sexual dysfunction in adult inpatients and outpatients with MDD. We included head-to-head RCTs of at least six weeks' duration comparing SGAD. Since head-to-head evidence was lacking for many comparisons, we also included placebo-controlled trials. We also examined data from observational studies with ≥1000 study participants and follow-up of at least 12 weeks. To be eligible for inclusion, a study had to report any health outcome related to sexual dysfunction, either as an adverse event (spontaneously reported by patients, systematically elicited, openly inquired, or observed by study clinicians), or as patient-rated or expert-rated outcomes of sexual dysfunction prospectively measured by a specific, validated instrument. We excluded studies that both reviewers agreed did not meet eligibility criteria. Discrepancies were resolved by discussion between both reviewers or, when necessary, by involving a third reviewer

(see Electronic Supplementary Material 1 for information on characteristics of included studies, and Electronic Supplementary Material 2 for information on the Update search strategy).

2.2.Quality Assessment and Data Extraction

Two trained reviewers (two at a time out of UR, AG, BN, MVN) independently abstracted data from each study and assigned an initial risk of bias (quality) assessment using predefined criteria based on those developed by the Cochrane Collaboration (low, moderate, and high risk of bias) [21]. To assess the risk of bias in observational studies, we used criteria outlined by Deeks and colleagues [22]. Any disagreement was resolved by consensus between the respective two reviewers. A senior reviewer (one at a time out of GG, LCM, RAH, LL, BNG) evaluated completeness of data abstraction and confirmed the quality assessment. If disagreements occurred, they were resolved by consensus. We abstracted information on study characteristics (study design, eligibility criteria), intervention (drugs, dose, duration), study participants, sample size, loss to follow-up, withdrawals because of adverse events, method of determining and reporting harms-related data and outcomes associated with sexual dysfunction. We used the Evidence-based Practice Center approach, conceptually similar to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, to assign an overall grade for strength of evidence (low, moderate, or high strength of evidence) of the outcome [23].

2.3.Data Synthesis and Analyses

To be included in the quantitative analysis, studies had to provide sufficient data to calculate measures of incidence of sexual dysfunction. We recalculated rates of sexual dysfunction for each study using the number of all randomized patients as the denominator to reflect a true intention-to-treat (ITT) analysis. For statistical reasons we combined all reported subtypes of sexual dysfunction (e.g. anorgasmia, ejaculation failure, ejaculation disorder, erectile dysfunction, delayed ejaculation, abnormal orgasm, decreased libido and loss of libido) into one outcome category of sexual dysfunction. When available, sex-specific rates were abstracted.

We conducted a network meta-analysis using Bayesian methods to compare rates of sexual dysfunction between SGAD, including both head-to-head trials comparing active interventions and placebo-controlled comparisons. To be included in the network meta-analysis, RCTs had to fulfill (1) the general study eligibility criteria, and (2) the statistical conditions required for network meta-analysis (consistency, heterogeneity, geometry of treatment network). We used the methods developed and illustrated in NICE Technical Support Document 2, which details the generalized linear modeling framework for network meta-analyses of RCTs [24]. We used a random effects logistic regression model adjusting for correlations between multiple-arms within each study. Study effect and outcome effect parameters were modeled by noninformative (flat) prior distributions that were normal (0, 10000). For the heterogeneity of the random-effects model, we used a uniform prior distribution centered at zero with sufficiently large variance. The first 20,000 simulations were discarded to allow for model convergence

and then a further 100,000 simulations were used in estimating the posterior probabilities. Convergence was verified by trace plots and inspection of the Gelman-Rubin statistic for monitored parameters. Our outcome measure was adverse events of sexual dysfunction. To assess the consistency between the different reporting methods, we conducted a sensitivity analysis, including studies where sexual dysfunction was determined only by open question or spontaneous patient reports. The network meta-analysis was performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) methods. We calculated odds ratios and 95% credible intervals (CrI) for all possible pairwise comparisons among our drugs of interest. We analyzed RCTs reporting only male-specific rates separately from RCTs reporting total rates of sexual dysfunction. Only a small number of trials included in the network meta-analysis reported sex-specific rates. We used all data from these trials combining male and female rates into total rates along with data from trials reporting total rates of sexual dysfunction only.

We conducted descriptive analyses, when conditions to perform comparative analyses could not be met. For studies providing only sex-specific rates of sexual dysfunction, we calculated weighted mean rates and 95% confidence intervals on sex-specific rates of sexual dysfunction pooling data from arms of both the active drug comparator and placebo-controlled trials. We calculated all descriptive analyses using StatsDirect Statistical Software, version 2.7.9 (StatsDirect, Cheshire, United Kingdom). Due to differences in study design, we could not pool rates from all observational studies and also present rates from individual studies. For both, the descriptive analyses and the network meta-analysis, we also included RCTs that did not report any baseline assessment of sexual dysfunction.

3. Results

Our searches identified 4,476 citations (see PRISMA flow-diagram, Fig. 1) [25] for the larger comparative effectiveness review on SGAD. We screened 1,532 full text articles for eligibility; of these, 63 studies of low and moderate risk of bias (58 RCTs, five observational studies) reporting data on any sexual dysfunction outcome or adverse event met our inclusion criteria for analysis. The majority of experimental trials were of six to eight weeks in duration.

Adverse events reporting and determination of sexual dysfunction varied widely among studies. Specific methods included prospective, systematically monitored and validated instruments to measure sexual function, rating scales, or structured clinical interviews to diagnose sexual dysfunction. Additionally, study authors relied on adverse events gathered by spontaneous patient reports, or using open questions or generic checklists by clinicians. In 22 of 58 (37.9%) RCTs, study authors did not provide any information on the method to collect adverse event data or determine sexual dysfunction. Only 14 of 58 (24.1%) RCTs reporting sexual dysfunction outcomes or adverse events reported a specific method to determine adverse events or outcomes of sexual dysfunction. In seven of 16 RCTs, study authors used a standardized validated instrument to establish sexual dysfunction at baseline and during the study period; however, they did not provide sufficient data in the published article to calculate sexual dysfunction outcomes.

All of the observational studies with data on sexual function outcomes reported the method to ascertain sexual dysfunction or adverse event; three of the five used a validated sexual function instrument (the Changes in Sexual Functioning Questionnaire; the Arizona Sexual Experience Scale; the Psychotropic-Related Sexual Dysfunction Questionnaire).

3.1. Evidence of risk of sexual dysfunction in patients with MDD from RCTs

Our analyses (quantitative or descriptive) included 58 RCTs of low or moderate risk of bias with information on sexual dysfunction, representing approximately 19,000 patients treated with SGAD.

3.1.1. Network meta-analysis

We conducted network meta-analyses of adverse events of sexual dysfunction using data from placebo-controlled or head-to-head trials. Of the 58 RCTs fulfilling the study eligibility criteria we could finally include 37 RCTs [26-62] meeting the statistical requirements for network meta-analysis. Overall, 14,576 patients were randomly assigned to placebo or one of the eleven included SGAD drugs. Twenty-two studies were two-arm trials, eleven were three-arm trials involving two different active comparisons and placebo, and four were multi-arm trials involving two or more active compounds at various dosages and placebo. The network of all included pairwise comparisons is shown in Fig. 2.

The full model random effects network meta-analysis included 66 pairwise comparisons (55 active SGAD pairwise comparisons and 11 placebo-controlled comparisons). We found statistically significant differences in adverse events of sexual dysfunction in 14 of the pairwise active comparisons (Table 1). Most comparisons showed a similar risk of sexual dysfunction among included SGAD; however, credible intervals were wide and included differences that would be considered clinically relevant. Eight individual comparisons present a statistically significantly higher risk of sexual dysfunction of one drug over another.

Nevertheless, three main patterns emerged (see Fig. 3): (1) Bupropion had a statistically significantly lower risk of sexual dysfunction than some other SGAD (escitalopram, paroxetine, and sertraline). (2) Escitalopram showed a statistically significantly higher risk of sexual dysfunction than some other SGAD (fluoxetine, mirtazapine, and nefazodone). (3) Paroxetine had a statistically significantly higher risk of sexual dysfunction than some other SGAD (fluoxetine, mirtazapine, nefazodone, and venlafaxine).

Convergence was satisfied in the full model, but not fully satisfactory for citalopram-comparisons in the model including only trials where sexual dysfunction was spontaneously reported by patients or elicited by open question. Findings of the sensitivity analyses assessing the impact of the method used to determine sexual

dysfunction in the network meta-analysis model were somewhat conflicting in that consistency between the different reporting methods could not always be confirmed.

Because of the indirect nature of the comparisons, the often wide credible intervals, and the high variation in magnitude of outcome, we rated the overall strength of evidence with respect to our findings low.

3.1.2. Descriptive analysis using data of trials reporting only sex-specific rates of sexual dysfunction

Due to reasons of heterogeneity, we did not combine direct and indirect evidence for pairwise comparisons from the trials reporting only sex-specific incidence of sexual dysfunction. Instead, we performed descriptive analysis calculating weighted mean rates pooling data both from active comparator and placebo-controlled trials. Overall, we used data from 21 RCTs [63-83] providing sex-specific rates of sexual dysfunction from 4,159 patients including six different SGAD (44 study arms: 34 active arms, 10 placebo-controlled arms).

We analyzed sex-specific rates separately and required a minimum of two trials to calculate weighted mean rates (WMR). Only trials reporting male-specific rates of sexual dysfunction provided sufficient data to allow calculation of WMR. Figure 4 summarizes by specific drug, the WMR of sexual dysfunction based on male-specific rates and 95 percent confidence intervals (95% CI) in patients with MDD reported in RCTs of SGAD. Across all trials reporting male-specific rates, the WMR of sexual dysfunction was 12.3 percent (95% CI 8.8 to 15.8), with a range of 8.8 percent of sexual dysfunction for fluoxetine (95% CI 0.5 to 17.0) and 15.8 percent for sertraline (95% CI 1.2 to 30.4). Overall, rates of sexual dysfunction did not differ among duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.

3.2. Evidence of sexual dysfunction in patients with MDD from observational studies

Descriptive analysis of tolerability used data from almost 7,200 study participants using SGAD (with a total of n=10 different drugs). We were able to include five observational studies providing data on sexual dysfunction: three prospective cohort studies [14, 84, 85], one prescription-event monitoring database study, [86] and one cross-sectional survey [87]. Except for the study by Mackay and co-authors [86] and the one by Meijer and colleagues [84], standardized validated instruments to ascertain sexual dysfunction at baseline and throughout follow-up were used. All of the five studies were conducted in various international outpatient settings. We present crude rates and incidence density rates of individual studies separately.

Table 2 summarizes, by specific drug, the incidence and prevalence of sexual dysfunction reported in three prospective cohort studies of SGAD in patients with MDD. Due to differences in study design and patient follow-up we did not calculate pooled weighted mean rates. Instead, rates from the individual studies are shown. In two of these prospective studies [14, 85] incidence rates at six months of follow-up were used.

The rates reported by Clayton et al. [87] refer to prevalence data from a cross-sectional study using data of a subsample of patients free of other possible causes of sexual dysfunction, yet with a wide range of treatment duration.

Rates of sexual dysfunction tended to be higher than those reported in RCTs. Overall, the weighted mean incidence of sexual dysfunction across all observational studies was 40.4 percent (95% CI 28.3% to 52.6%). Reported rates by specific drug ranged from 7.0 percent prevalence for bupropion in a cross-sectional study [87] to a 72.7 percent six-month-incidence for citalopram in a prospective cohort study [14]. Both studies relied on validated instruments to ascertain sexual function, although only the study by Montejo et al. established a cohort free of sexual dysfunction at the outset [14]. Six-month-incidence rates tended to be higher than the prevalence rates gathered from the cross-sectional survey (citalopram 72.7% vs. 30.0%, fluoxetine 57.7% vs. 23.0%, paroxetine 70.7% vs. 25.0%, sertraline 62.9% vs. 25.0%, and venlafaxine 67.3% vs. 30.0%, respectively). Duenas et al. reported a six-month incidence rate of 23.4% for duloxetine in outpatients from a prospective cohort study including only sexually active patients without sexual dysfunction at study enrolment [85].

Due to differences in study design, rates of sexual dysfunction from two additional observational studies could not be pooled with the ones from the above mentioned three prospective cohort studies. Incidence density rates, which adjust for time of exposure, reported in the individual studies were converted and are shown in table 3. From a prescription-event monitoring database study [86], adverse events of only male sexual dysfunction (impotence or ejaculation failure) were recorded showing a rate of 9.6 per 1000 person-years for nefazodone, and 30 per 1000 person-years for paroxetine. Sexual dysfunction adverse events for sertraline in a prospective observational study [84] were reported as number of first adverse events per 1000 person-years, yet study authors did not ascertain participants' baseline status of sexual function prior to antidepressant medication. Patients were followed for an average duration of 5.7 months (range one to 365 days). Reported rates were higher for men than for women (loss of libido 31/1000 person-years; ejaculation failure 14/1000 person-years; impotence 9/1000 person-years; other male sexual function disorder 4/1000 person-years; female anorgasmia 6/1000 person-years; other female sexual function disorder 3/1000 person-years).

4. Discussion

In this systematic review with data from sixty-three studies of low and moderate risk of bias (58 RCTs, five observational studies) with more than 26,000 patients treated with SGAD, we found some variation in sexual dysfunction associated with SGAD across drugs, yet no consistent differences between drugs. The methods used to assess adverse events varied considerably in efficacy trials with about a third of the trials included in our analysis providing no information on how harms-related data was collected or how sexual function was assessed, and only a fifth of the trials using a specific method or instrument to determine sexual dysfunction. We rated the overall strength of evidence low, indicating a low confidence that the evidence reflects the true effect.

In our network meta-analyses, most comparisons showed a similar risk of sexual dysfunction among included SGAD. Credible intervals, however, were wide and included differences that would be considered clinically relevant. Since we conducted multiple comparisons and found differences in the method sexual dysfunction was defined and reported in individual trials, these results should be interpreted cautiously. Nevertheless, we observed three main patterns: Bupropion had a statistically significantly lower risk of sexual dysfunction than some other SGAD, and both escitalopram, and paroxetine showed a statistically significantly higher risk of sexual dysfunction than some other SGAD.

Our findings of varying rates of adverse events are consistent with previous studies. Authors of a systematic review and meta-analysis using data from 234 studies with direct and indirect comparisons of SGAD found no substantial differences in efficacy for the treatment of MDD, however, differences were found with respect to onset of action, frequency of adverse events and rates of discontinuation [11]. With respect to the observed lower risk of sexual dysfunction for bupropion, our findings are consistent with a previous systematic review and meta-analysis comparing sexual adverse events of bupropion and three SSRIs (fluoxetine, paroxetine, sertraline) which found bupropion causing significantly less sexual dysfunction than the comparator drugs while having similar effectiveness [15], a finding that was later replicated in a US-cross-sectional study [87] and by authors of a comparative effectiveness review and meta-analysis [11]. That patients treated with bupropion experience less frequent treatment-emergent sexual dysfunction has been explained with the lack of serotonergic activity of this drug (a selective norepinephrine and dopamine reuptake inhibitor). We found mirtazapine to be associated with a lower risk of sexual dysfunction in some pairwise comparisons. Mirtazapine, classified a noradrenergic and specific serotonergic antidepressant, has been described to have minimum effects on monoamine reuptake and was shown to be less likely associated with sexual adverse events compared to SSRIs (fluoxetine, paroxetine, sertraline) [17].

As to the results of the descriptive analyses, we cannot draw firm conclusions about the comparative harms of second-generation antidepressants. Using data from all trials reporting male-specific rates, rates of sexual dysfunction did not differ among included SGAD. We observed lower rates of sexual dysfunction across trials reporting only sex-specific rates as compared to those reported in observational studies. Underscoring the validity of the estimate of sexual dysfunction associated with antidepressants reported in observational studies is the use of prospectively defined populations free from sexual dysfunction at baseline and the prospective assessment of sexual function with standardized and validated instruments. Conversely, the majority of the efficacy trials included in our analysis did not include such study procedures, thus making it difficult to establish treatment-emergent sexual dysfunction.

We found reporting of adverse events related to sexual dysfunction in some of the RCTs included in our analysis inconsistent and insufficient. In the majority of trials, investigators did not specify how harms-related information was gathered: definitions of adverse events of sexual dysfunction were often not explicit and clear; also,

investigators sometimes relied on scales to assess sexual function that lacked appropriate instrument development and validation. Additionally, authors often did not state the time frame of surveillance for adverse events thus not specifying whether recording of adverse events occurred retrospectively or prospectively; also, only collecting data on adverse event for some time after the study intervention can capture longer latency. Only rarely did authors provide information on reasons for discontinuations and withdrawals due to adverse events. In none of the included RCTs did authors report on whether attribution of a specific cause was blinded to the assigned treatment. Also, it was difficult to establish from the data of the individual studies whether or how study investigators combined data for different subsets of sexual dysfunction adverse events into one outcome measure. Also, sexual dysfunction as a harm of second-generation antidepressant treatment was chosen as a major primary outcome in only a minority of included studies and authors did not describe a-priori plan of statistical analysis. Problems of low power for uncommon events or adjustment for multiple outcomes were not addressed. Due to these shortcomings by investigators of individual trials included in our analysis, comparison of rates of sexual dysfunction, particularly from efficacy trials, must be made with great caution.

Our study has several limitations. Selection of studies was limited to English-language publications only. We did not account for observed differences in medication dosages, study duration or any confounding from use of concomitant medications or comorbid conditions potentially affecting sexual function. The majority of included RCTs were of short duration so that an estimation of long-term effects of treatment-emergent sexual dysfunction is not possible. Also, we included RCTs that did not report any baseline assessment of sexual dysfunction. Thus, the reported rates sexual dysfunction in these trials might have been inflated. Furthermore, only a small number of trials included in the network meta-analysis reported sex-specific rates so we did not perform sex-specific analyses. Although type, severity and clinical course of sexual dysfunction associated with antidepressant treatment can vary by gender [88], we were not able to assess the potential impact of gender on estimated sexual dysfunction adverse events. Results of both the network meta-analyses and the descriptive analyses should therefore be interpreted with caution. Network meta-analysis is a method that combines direct and indirect information across a network of RCTs and provides estimates of the (adverse) effect of each intervention relative to each other, whether or not they have been directly compared in trials, yet the key assumption is consistency between direct and indirect estimates of effect [89]. We cannot completely rule out that observed differences across trials might be due to violations of consistency assumptions. Still, in the absence of sufficient head-to-head evidence, network meta-analysis can serve as an additional tool to synthesize multiple treatments.

The onset of treatment-emergent sexual dysfunction or aggravation of a preexisting sexual dysfunction may add to the distress of a patient with MDD, diminish the patient's quality of life, lead to the discontinuation of antidepressant treatment and also threaten the doctor-patient relationship, particularly if the patient has not been fully informed of such adverse events of second-generation antidepressants [90]. Since evidence suggests that SGAD largely have similar efficacy, onset of action and specific adverse events

profiles should guide a clinician's choice of a specific drug for an individual patient. Given the impact of sexual dysfunction on a patient's quality of life, clinicians should provide patients with all relevant information on possible sexual adverse events of a particular antidepressant and discuss patients' preferences and values before initiating antidepressant therapy. If patients are concerned about maintaining normal sexual functioning (e.g. younger patients), the decision of choosing an antidepressant that is less likely to be associated with sexual dysfunction should be discussed.

5. Conclusions

Based on the findings of this review using data from RCTs and observational studies on adverse events and second-generation antidepressants, the comparative risk of sexual dysfunction associated with a specific antidepressant cannot be precisely determined. Nevertheless, we observed three main patterns in our network meta-analysis with bupropion having a statistically significantly lower risk of sexual dysfunction than some other SGAD, and both escitalopram, and paroxetine showing a statistically significantly higher risk of sexual dysfunction than some other SGAD. Clinicians should routinely discuss the possibility of sexual dysfunction as adverse events of second-generation antidepressants and take into account patients' preferences when selecting an antidepressant and monitoring treatment. Further, we found inconsistencies and shortcomings in methods to determine and report adverse events of sexual dysfunction in many of the studies included in this review, thus potentially contributing to biased estimates. Future studies on SGAD should be adequately powered to provide complete, reliable, accurate and gender-specific information on adverse events and should be designed and conducted using systematic and valid methods to assess sexual dysfunction adverse events. Also, reporting quality of adverse events of sexual dysfunction in published trials should be improved to help researchers better appraise results of such trials and clinicians inform patients accordingly.

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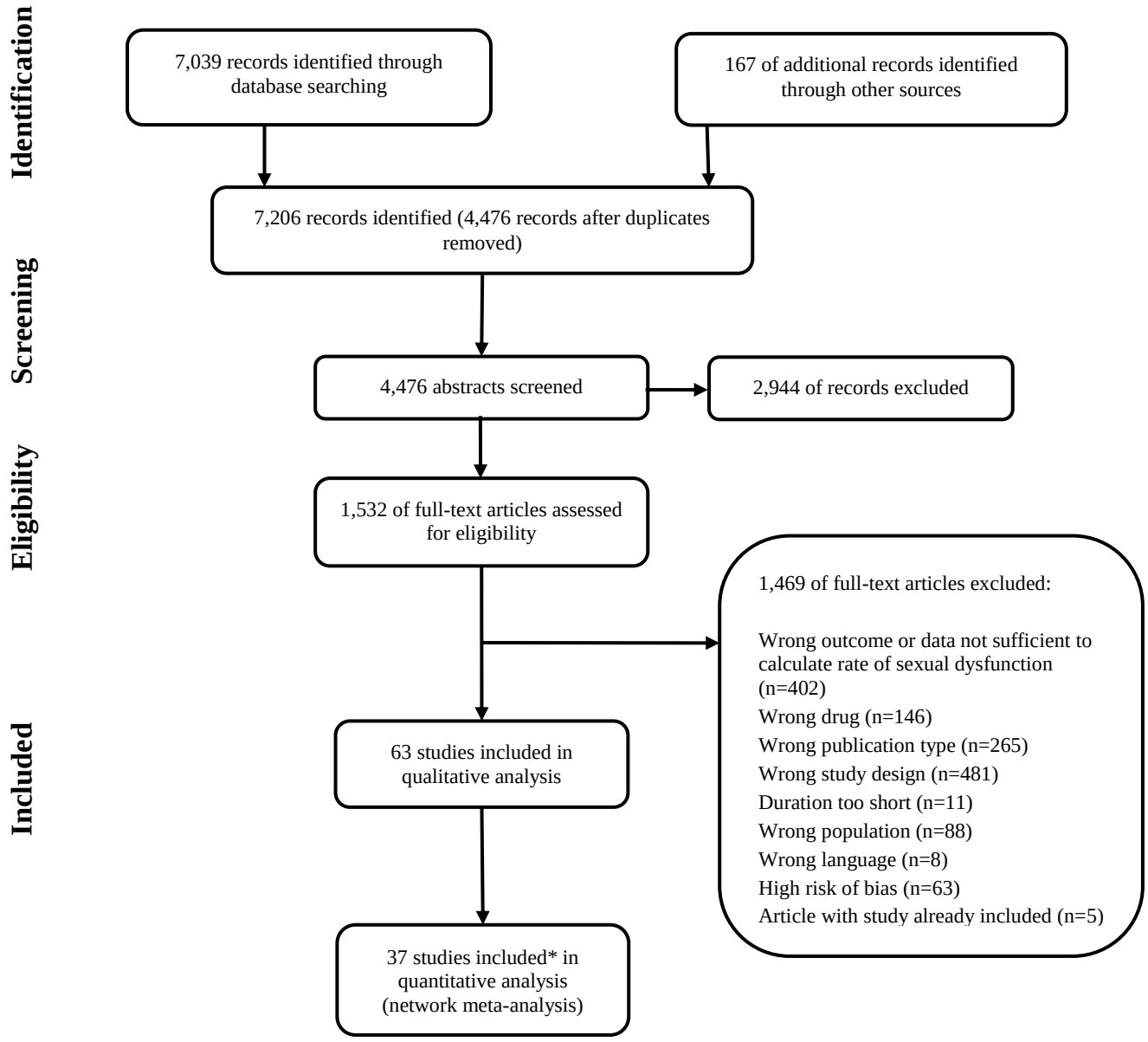
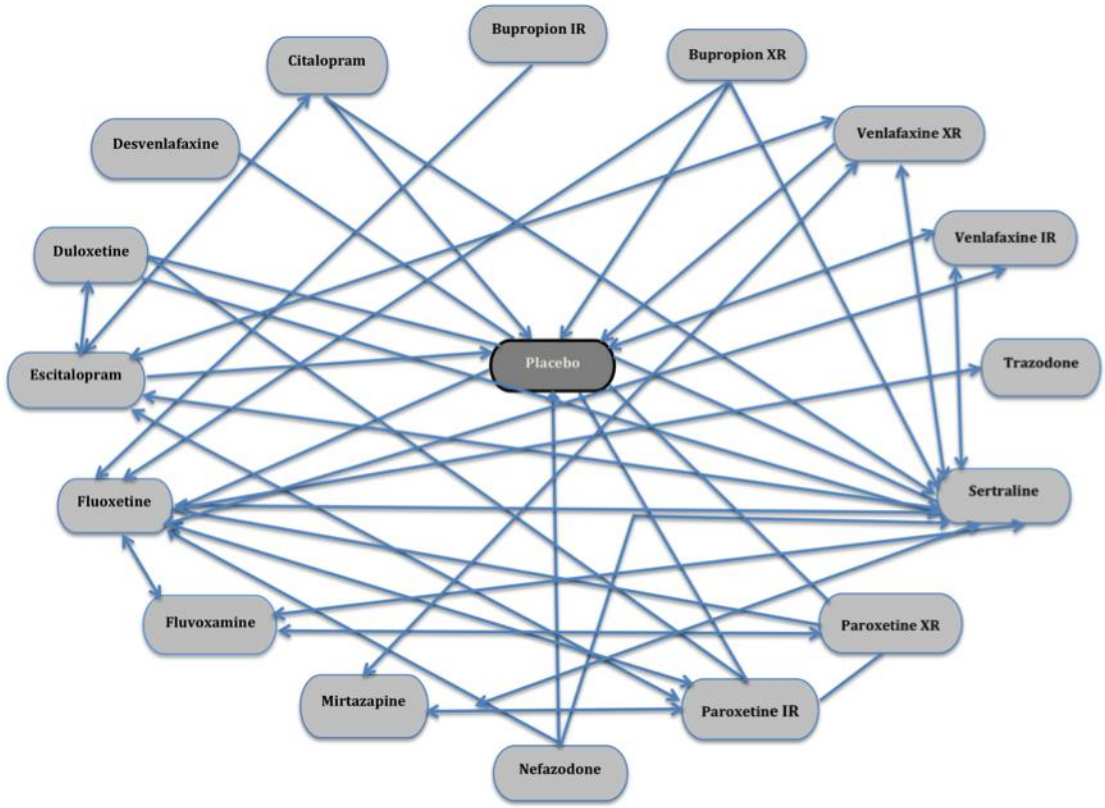
Network meta-analyses were conducted by Tania Wilkins, PhD (The University of North Carolina at Chapel Hill, Gillings School of Global Public Health Biostatistics, 3101 McGavran-Greenberg Hall, Chapel Hill, NC 27599-7420).

Fig. 1 Flow diagram: summary of evidence search and selection.



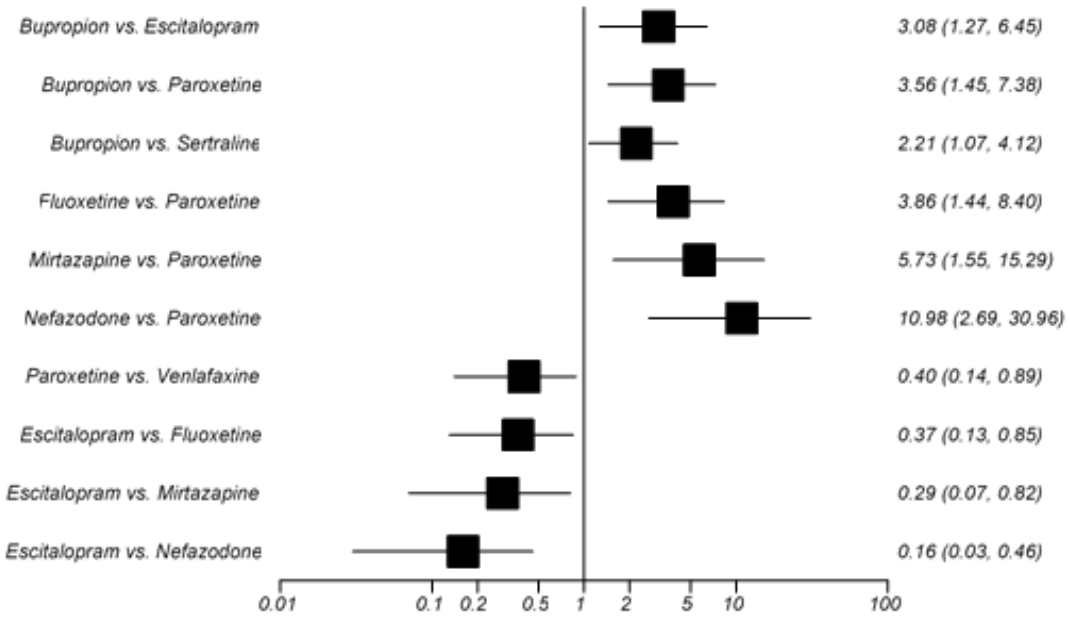
*RCTs were included in the network meta-analysis if they fulfilled (i) general study eligibility criteria, and (ii) statistical requirements for network meta-analysis. *RCTs* randomized controlled trials

Fig. 2 Network of all included comparisons for the network meta-analysis of sexual dysfunction associated with second-generation antidepressants.



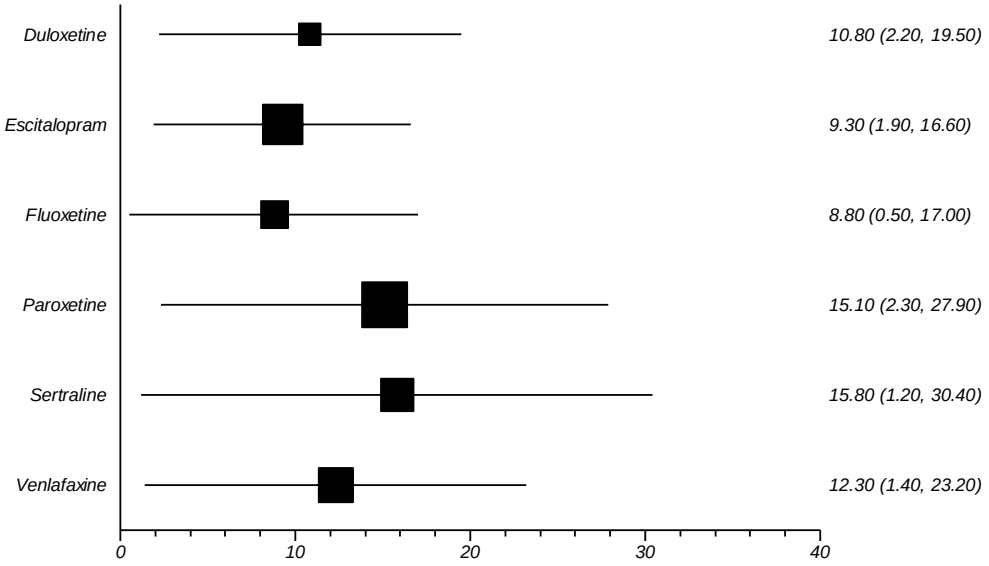
IR: immediate release; *XR*: extended release

Fig. 3 Results of network meta-analysis of sexual dysfunction for selected pairwise second-generation antidepressants comparisons, odds ratios.



* Odds ratios <1 indicate a higher rate of sexual dysfunction of the drug listed on the *left-hand side* ('first drug'); ** Odds ratios >1indicate a higher rate of sexual dysfunction of the drug listed on the *right-hand side* ('second drug'); selected results from full model of random effects network meta-analysis. *SD* sexual dysfunction

Fig. 4 Male-specific weighted mean rates of sexual dysfunction from individual randomized controlled trials



Data are presented as % (95 % confidence intervals). Weighted mean rates (%) calculated using drug-specific rates of sexual dysfunction from individual randomized controlled trials pooling data from active-comparator trials and placebo-controlled trials. Rates were calculated only if data from at least two trials were available (only male-specific rates could be calculated; we did not use data from a small RCT for desvenlafaxine and trazodone, respectively). Comparisons across drugs must be made cautiously: method and extent of adverse event assessment differed across studies.

Table 1 Odds ratio of sexual dysfunction (95 % credible intervals for pairwise comparisons, mixed-treatment comparison)[a]

Pairwise comparisons	OR of sexual dysfunction[a]	(95% CrI)
Bupropion vs. Citalopram	2.94	(0.81-7.90)
Bupropion vs. Duloxetine	2.21	(0.88-4.67)
Bupropion vs. Escitalopram	3.08	(1.27-6.45)
Bupropion vs. Fluoxetine	1.02	(0.42-2.11)
Bupropion vs. Fluvoxamine	1.35	(0.24-4.44)
Bupropion vs. Mirtazapine	0.82	(0.20-2.29)
Bupropion vs. Nefazodone	0.45	(0.10-1.29)
Bupropion vs. Paroxetine	3.56	(1.45-7.38)
Bupropion vs. Sertraline	2.21	(1.07-4.12)
Bupropion vs. Venlafaxine	1.30	(0.47-2.93)
Citalopram vs. Duloxetine	0.96	(0.26-2.51)
Citalopram vs. Escitalopram	1.31	(0.41-3.15)
Citalopram vs. Fluoxetine	0.46	(0.11-1.30)
Citalopram vs. Fluvoxamine	0.59	(0.08-2.16)
Citalopram vs. Mirtazapine	0.36	(0.06-1.17)
Citalopram vs. Nefazodone	0.20	(0.03-0.66)
Citalopram vs. Paroxetine	1.57	(0.41-4.13)
Citalopram vs. Sertraline	0.96	(0.30-2.32)
Citalopram vs. Venlafaxine	0.57	(0.14-1.60)
Duloxetine vs. Escitalopram	1.50	(0.68-2.93)
Duloxetine vs. Fluoxetine	0.52	(0.18-1.18)
Duloxetine vs. Fluvoxamine	0.67	(0.12-2.17)
Duloxetine vs. Mirtazapine	0.41	(0.10-1.13)
Duloxetine vs. Nefazodone	0.22	(0.05-0.64)
Duloxetine vs. Paroxetine	1.72	(0.81-3.20)
Duloxetine vs. Sertraline	1.11	(0.48-2.25)
Duloxetine vs. Venlafaxine	0.65	(0.22-1.51)
Escitalopram vs. Fluoxetine	0.37	(0.13-0.85)
Escitalopram vs. Fluvoxamine	0.48	(0.08-1.58)
Escitalopram vs. Mirtazapine	0.29	(0.07-0.82)
Escitalopram vs. Nefazodone	0.16	(0.03-0.46)
Escitalopram vs. Paroxetine	1.26	(0.50-2.58)
Escitalopram vs. Sertraline	0.79	(0.39-1.54)
Escitalopram vs. Venlafaxine	0.47	(0.16-1.08)
Fluoxetine vs. Fluvoxamine	1.49	(0.24-5.07)
Fluoxetine vs. Mirtazapine	0.89	(0.20-2.60)
Fluoxetine vs. Nefazodone	0.49	(0.10-1.50)
Fluoxetine vs. Paroxetine	3.86	(1.44-8.40)
Fluoxetine vs. Sertraline	2.44	(0.94-5.26)
Fluoxetine vs. Venlafaxine	1.41	(0.47-3.30)
Fluvoxamine vs. Mirtazapine	0.96	(0.12-3.60)
Fluvoxamine vs. Nefazodone	0.52	(0.06-2.01)
Fluvoxamine vs. Paroxetine	4.08	(0.81-12.73)
Fluvoxamine vs. Sertraline	2.59	(0.53-7.98)
Fluvoxamine vs. Venlafaxine	1.54	(0.25-5.29)
Mirtazapine vs. Nefazodone	0.73	(0.11-2.56)
Mirtazapine vs. Paroxetine	5.73	(1.55-15.29)
Mirtazapine vs. Sertraline	3.62	(1.01-9.59)
Mirtazapine vs. Venlafaxine	2.03	(0.57-5.31)
Nefazodone vs. Paroxetine	10.98	(2.69-30.96)
Nefazodone vs. Sertraline	6.89	(1.81-18.89)
Nefazodone vs. Venlafaxine	4.11	(0.84-12.70)
Paroxetine vs. Sertraline	0.68	(0.30-1.35)
Paroxetine vs. Venlafaxine	0.40	(0.14-0.89)
Sertraline vs. Venlafaxine	0.61	(0.25-1.24)

a Relative treatment effect of each treatment relative to reference comparator expressed as OR (with 95 % CrI). An OR <1 indicates a higher rate of SD of the drug listed on the left-hand side ('first drug'); an OR >1 indicates a higher rate of SD of the drug listed on the right-hand side ('second drug'). Method and extent of adverse event assessment differed across studies; comparisons across drugs must be made cautiously. Based on random-effects network meta-analysis using Bayesian methods. *CrI* credible interval, *OR* odds ratio, *SD* sexual dysfunction

Table 2 Prevalence/Incidence of sexual dysfunction from three observational studies (crude rates as percentages from individual studies)

Drug	Sexual dysfunction (mean percentage)	Study design	N included in analysis
Bupropion	7.0	cross-sectional survey[a]	45
Citalopram	30.0	cross-sectional survey[a]	83
	72.7	prospective study[b]	66
Duloxetine	23.4	prospective study[c]	406
Fluoxetine	23.0	cross-sectional survey[a]	245
	57.7	prospective study[b]	279
Fluvoxamine	62.3	prospective study[b]	77
Mirtazapine	24.4	prospective study[b]	49
Nefazodone	8.0	prospective study[b]	50
Paroxetine	25.0	cross-sectional survey[a]	159
	70.7	prospective study[b]	208
Sertraline	25.0	cross-sectional survey[a]	161
	62.9	prospective study[b]	159
Venlafaxine	30.0	cross-sectional survey[a]	70
	67.3	prospective study[b]	55

MDD major depressive disorder, *SD* sexual dysfunction,

a Prevalence rates; patients with MDD; subsample with patients free of other possible causes of SD; length of treatment varied (1% < a week; 24% more than a week but less than 3 months; 17% more than 6 months but less than 12 months; 28% one to three years; 12% more than 3 years);[87]

b Incidence rates calculated at 6 months of follow-up in participants free of SD prior to antidepressant medication;[14]

c Incidence rates calculated at 6 months of follow-up in sexually active patients without SD at study enrolment;[85]

Table 3 Incidence density rate of sexual dysfunction from two observational studies

Drug	Sexual dysfunction (incidence density rates)	Study design	N included in analysis
Nefazodone	9.6/1000 PY	prescription-event monitoring, database study[a]; only male SD (impotence or ejaculation failure), 1 study	4418
Paroxetine	30/1000 PY	prescription-event monitoring, database study[a]; only male SD (impotence or ejaculation failure), 1 study	4373
Sertraline	loss of libido 31/1000 PY; ejaculation failure 14/1000 PY; impotence 9/1000 PY; other sexual function disorder (male) 4/1000 PY; anorgasmia (female) 6/1000 PY; other sexual function disorder (female) 3/1000 PY	prospective observational study[b], 1 study	659

PY person years, *SD* sexual dysfunction

a Unclear whether study participants were free of SD prior to antidepressant medication; SD recorded in patients record after the date of first prescription;[86]

b Unclear whether study participants were free of SD prior to antidepressant medication; SD adverse events were ascertained by open question by clinician; start and stop dates of the events and assessment of severity ('mild', 'moderate' or 'severe') were recorded; patients were followed for an average duration of 5.7 months (range 1–365 days)[84]

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Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder - Results from a Systematic Review with Network Meta-Analysis. *Drug Safety*; U. Reichenpfader, G. Gartlehner, L.C. Morgan, A. Greenblatt, B. Nussbaumer, R. A. Hansen, M. Van Noord, L. Lux, and B. N. Gaynes. **Corresponding author:** U. Reichenpfader, Department for Evidence-based Medicine and Clinical Epidemiology, Krems, Austria; Department of Medical and Health Sciences - Division of Community Medicine, Linköping University, Sweden; ureichenpfader@hotmail.com

Electronic Supplementary Material 1:

Table S1. Characteristics of Included Studies

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author, Year Alvarez et al, 2012 [1] **Country and Setting** multinational, multicenter **Funding** H. Lundbeck A/S	**Research objective** To evaluate efficacy, safety, and tolerability of Lu AA21004 vs. placebo using venlafaxine XR as active reference in patients with DSM-IV-TR major depressive disorder (MDD) **Drugs, Doses, and Range** D1: PBO D2: VENLA XR (225 mg 1 x daily) **Fixed dose** Yes **Flexible dose** No **Study design** phase II RCT, double blinded **Duration** 6 weeks **Type of depression** MDD **Intervention** D1: PBO D2: Venlafaxine XR	**Inclusion criteria:** • Adults (age range): 18-65 years • Diagnosed with MDD according to DSM-III or -IV: Current epidsode of MDD with at least 3 months' duration • MADRS: total score ≥30 at baseline visit **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: • current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition • Patients at serious risk of suicide, based on the	**Groups similar at baseline** Yes **n =** D1: 105 D2: 114 Overall: 219 **Mean age, years** D1: 42.0 D2: 45.0 **Sex, % female** D1: 65.7 D2: 54.9 **Race, % white** D1: 93.3 D2: 92.0 Overall: NR **Baseline MADRS** D1: 33.9 D2: 34.2 Overall: NR **Baseline HAMD-24** D1: 29.7 D2: 29.4 Overall: NR	D1: 2/105 (1.9%) D2: n=3 of women reported AE related to SD (3/62, 4.8% of women); n=11 of men reported AE related to SD (11/51, 21.6% of men); overall % with SD 14/114 (12.3%); #AE reported: anorgasmia 7/51(13.7% of men); ejaculation delayed 4/51 (7.8% of men); erectile dysfunction 4/51 (7.8% of men); 2 withdrawals due to SD (1 anorgasmia,1 delayed ejaculation);	non-leading question to ascertain AE; no targeted questions/ no specific instrument used to assess SD	**Risk of Bias:** low **Withdrawals due to adverse events, %** D1: 4 D2: 14 **Withdrawals due to lack of efficacy, %** NR

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
		investigator's clinical judgement, or who had a score of 5 on item 10 of the MADRS scale (suicidal thoughts) • any substance abuse disorder within the previous 6 months, • presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or • any Axis II disorder that might compromise their participation in the study Investigation **Outcome measures** • MADRS • Adverse events				

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Baldwin et al., 2006 [2] **Country and Setting** multinational, multicenter **Funding** H. Lundbeck A/S	**Research objective** To evaluate short- and long-term antidepressant tolerability and efficacy of ESC and PAR. **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): low-high; 10-20 mg D2: PAR (10-60 mg 1 x daily): medium; 20-40 mg **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** Yes **Study design** RCT **Duration** 8 weeks (includes both acute and maintainence periods) **Type of depression** MDD **Intervention** D1: PAR D2: ESC	**Inclusion criteria:** • Adults (age range): 18 years old and over • Diagnosed with MDD according to DSM-III or -IV: Current epidsode of MDD • MADRS: 22 or greater and 40 or less **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: includes tryptophan, benzodiazepines, antipsychotics, psychoactive herbal remedies, MAOIs, prophylactic treatment dopamine antagonists • Schizophrenia, psychotic disorders, mania or hypomania, eating disorders, obsessive-compulsive disorder, bipolar disorder • Investigational drug use within last 3 months • MADRS item 10 score of 5 or greater	**Groups similar at baseline** Yes **n =** D1: 159 D2: 166 Overall: 325 **Mean age, years** D1: 45.1 D2: 44.9 Overall: 45 **Sex, % female** D1: 74.7 D2: 72.7 Overall: 75.0 **Race, % white** D1: 99.4 D2: 98.8 Overall: NR **Baseline HAM-A** NR Overall: NR **Insomnia, %** NR Overall: NR **Concomitant anergia, %** NR Overall: NR **Experienced prior depressive episodes, %** NR Overall: NR	ASEX scores, week 27%: D1: 57.7 (proportion of patients with sexual dysfunction (LOCF analysis) declined from baseline (67.3%) during both acute (61.2% at week 8) and maintenance treatment) D2: 57.0 (proportion of patients with sexual dysfunction (LOCF analysis) declined from baseline (69.9%) during both acute (64.1% at week 8) and maintenance treatment	ASEX	**Attrition** **Overall attrition, %:** 28 **Attrition rate, %:** D1: 34 D2: 21 **Study Quality:** Fair

	• Another Axis I disorder within previous 6 months • Learning disability • Cognitive disorder • Nonresponse or hypersensitivity to CIT and/or PAR • History of severe allergy or hypersensitivity • History of lactose intolerance • Antidepressants within 2 weeks before screening • Triptans, oral anticoagulants • Sildenafil citrate • Cimetidine • Type 1c anti-arrhythmics • Cardiac glycosides • Narcotic analgesics • Receiving formal psychotherapy **Outcome measures** • MADRS • Adverse events • Quality of life scales, ASEX scale

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author, Year Baldwin et al., 2012 [3] **Country and Setting** multinational, multicenter **Funding** H. Lundbeck A/S	**Research objective** To evaluate efficacy, safety, and tolerability of Lu AA21004 versus placebo, using duloxetine as active reference, in patients with DSM-IV-TR diagnosed major depressive disorder (MDD) **Drugs, Doses, and Range** D1: PBO D2: DUL (60 mg 1 x daily): medium; 20-40 mg **Fixed dose** Yes **Flexible dose** No **Study design** RCT, double blinded **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: PBO D2: DULOXETINE	**Inclusion criteria:** • Adults (age range): 18-75 years • Diagnosed with MDD according to DSM-III or -IV: Current epidsode of MDD with at least 3 months' duration • MADRS: total score ≥26 at both the screening and baseline visits **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: • current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition • Patients at serious risk of suicide, based on the investigator's	**Groups similar at baseline** Yes **n =** D1: 152 D2: 157 Overall: 309 **Mean age, years** D1: 43.4 D2: 45.3 **Sex, % female** D1: 69.6 D2: 67.7 **Race, % white** D1: 77.7 D2: 78.1 Overall: NR **Baseline MADRS** G1: 31.7 G2: 31.4 Overall: NR **Baseline HAM-A** G1: 23.1 G2: 22.8 Overall: NR	D1: 0 D2: N of men with sexual dysfunction Treatment-Emergent Adverse Events (anorgasmia, abnormal orgasm, decreased libido, ejaculation disorder, ejaculation failure, delayed ejaculation, erectile dysfunction, and increased erection): 7/52 (13.5% of men)	non-leading question to ascertain AE; no targeted questions/ no specific instrument used to assess SD **Comments** NR	**Risk of Bias:** Moderate **Withdrawals due to adverse events, %** D1: 8 D2: 11 **Withdrawals due to lack of efficacy, %** NR

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
		clinical judgement, or who had a score of 5 on item 10 of the MADRS scale (suicidal thoughts) • any substance abuse disorder within the previous 6 months, • presence or history of a clinically significant neurological disorder (including epilepsy), any neurodegenerative disorder, or • any Axis II disorder that might compromise their participation in the study Investigation **Outcome measures** • MADRS • Adverse events				

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Behnke et al., 2003[4] **Country and setting:** Multinational Multicenter **Funding:** NV Organon	**Research objective:** To compare onset of antidepressant efficacy of MIR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 346 **Intervention:** D1: MIR: 30-45 mg/d D2: SER: 50-150 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Epilepsy • History of seizure disorder or anti-convulsant treatment • Current eating disorders diagnosis • Previous postpartum depression or anxiety disorder diagnosis	**Mean age (yrs):** D1: 42 D2: 41 **Sex (% female):** D1: 55.7 D2: 61.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	CSFQ data not shown; AE: decrease: D1 1.1% D2: 5.9% *P* = 0.02 **Overall adverse events:** D1: 64 D2: 68	CSFQ; AE method NR	**Overall attrition rate:** 20.8% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Benkert et al., 2000[5] **Country and setting:** Germany Multicenter (50) **Funding:** Organon, GmBH, Munich, Germany	**Research objective:** Safety and efficacy of MIR and PAR in treatment of major depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 275 **Intervention:** D1: MIR: 15-45 mg/d (32.7) D2: PAR: 20-40 mg/d (22.9)	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Suicidal tendencies	**Mean age (yrs):** D1: 47.2 D2: 47.3 **Sex (% female):** D1: 63 D2: 65 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22.4 (3.3) D2: 22.4 (3.2)	D1: orgasmic dysfunction 3.1% D2: 13.5% P=0.048	UKU Side Effects Rating Scale	**Overall attrition rate:** 23% **Overall adverse events:** D1: 68.1 D2: 63.4 **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Bennie et al., 1995[6] **Country and setting:** UK Multicenter (20 centers) **Funding:** Pfizer, Inc	**Research objective:** To compare SER and FLUOX in outpatients with depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 286 **Intervention:** D1: SER: 50-100 mg/d D2: FLUOX: 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 49.9 D2: 49.9 **Sex (% female):** D1: 57.7 D2: 64.6 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.2 D2: 23.4	D1: male SD (ejaculation delayed, impotence/erectile dysfunction, reduced libido): 3/60 (5% of men) D2: male SD (ejaculation delayed, impotence/erectile dysfunction, reduced libido): 2/51 (3.9% of men)	spontaneously reported	**Overall attrition rate:** 13.3% **Overall adverse events:** D1: 56 D2: 60 **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Risk of Bias
Author: Bielski et al., 2004[7] **Country and setting:** United States Outpatient centers **Funding:** Forrest Laboratories, Inc	**Research objective:** To compare ESC and VEN XR in depressed outpatients at highest recommended doses in United States **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 198 **Intervention:** D1: ESC: 20mg D2: VEN: XR 225mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D24 > 20 • Normal physical exam, labs, and ECG (or any abnormality insignficant) • Using contraceptive **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with VEN or ESC • Failure to respond to adequate trials of 2+ antidepressants	**Mean age (yrs):** D1: 37.3 D2: 37.5 **Sex (% female):** D1: 69.4 D2: 47.0 **Race (% white):** D1: 77.6 D2: 73.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 28.6 (4.1) D2: 27.4 (4.5)	D1: ejaculation disorder 2/30 (6.7% of men) D2: ejaculation disorder 12/53 (22.6% of men)	NR	**Overall attrition rate:** 30% **Overall adverse events:** D1: 68 D2: 85 **ITT analysis:** Yes **Risk of Bias:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author, Year Boulenger et al., 2006[8] **Country and Setting** Multinational; psychiatric and primary care settings **Funding** H. Lundbeck A/S	**Research objective** To compare efficacy and tolerability of ESC (20 mg/day) and PAR (40 mg/day) in patients with severe MDD over a treatment period of 24 weeks and to investigate if treatment outcome for severely depressed patients depends on their baseline level of anxiety. **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): 20 mg 1 x daily; high D2: PAR (10-60 mg 1 x daily): 40 mg 1 x daily; medium **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **Duration** 24 weeks **Type of depression** MDD **Intervention**	**Inclusion criteria:** • Adults (age range): 18 to 75 years • Diagnosed with MDD according to DSM-III or -IV • MADRS: score greater than or equal 30 at baseline • Duration of depressive episode had to be more than 2 wks, but less than 1 yr **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Bipolar disorder, psychotic disorder or features, obsessive-compulsive disorder, current eating disorders (anorexia nervosa, bulimia), mental retardation, any pervasive developmental disorder or cognitive disorder • Illicit drug and alcohol abuse:	**Groups similar at baseline** Yes **n =** D1: 232 D2: 227 (For subgroup analysis of highly anxious patients: n=286) **Mean age, years** D1: 43.8 (12.5) D2: 44.7 (13.0) **Sex, % female** D1: 67 D2: 70 **Race, % white** D1: 97.8 D2: 99.6 **Baseline HAM-A** D1: 23.5 (7.5) D2: 23.5 (7.1) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Mean baseline MADRS total score	D1: 8% of men; erectile dysfunction (men): n=4 (of 153 with AE; (5.3% of men); ejaculation delayed (men), n=2 (2.7% of men) D2: 14.7% of men (ns); erectile dysfunction (men): paroxetine n=4 (of 162 with AE; 5.9% of men); escitalopram: n=4 (of 153 with AE; (5.3% of men); ejaculation delayed (men): paroxetine n=6 (of 162 with AE; 8.8% of men), escitalopram: n=2 (of 153 with AE; 2.7% of men)	spontaneously reported	**Overall adverse events, %:** D1: 7.8 D2: 15.4 **Study Quality:** Fair **Attrition** **Overall attrition, %:** 26.3 % attrition rate based on number of patients randomized, n= 459. **Attrition rate, %:** D1: 20,3 D2: 32,6 **Withdrawals due to adverse events, %** D1: 7.8 D2: 15.4 **Withdrawals due to lack of efficacy, %** D1: 4.3 D2: 6.2 **Comments** The calculations were based on number of patients randomized (Overall n= 459; ESC 20 mg/day n= 232, PAR 40 mg/day n= 227). Significantly more patients ($P < 0.01$) withdrew from PAR

	D1: ESC 20 mg/day D2: PAR 40 mg/day	within 12 months • ECT within last: 6 months • Suicidal tendencies • History of lactose intolerance • History of hypersensitivity or non-response to CIT, ESC or PAR. • Score ≥ 5 on item 10 of MADRS scale • Those who were receiving formal behaviour therapy or systematic psychotherapy **Outcome measures** • HAM-D • MADRS: total score mean change from baseline to week 24 • CGI-S or CGI-I • Quality of life scales • HAM-A	was approximately 35 in both treatment groups, indicating a severely to very severely depressed population.		group than from ESC group.

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Burke et al., 2002 [9] **Country and setting:** United States Multicenter (35 centers) **Funding:** Forest Laboratories	**Research objective:** To evaluate efficacy and tolerability of ESC in treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 369 **Intervention:** D1: PBO D2: ESC 10 mg/d D3: ESC 20 mg/d D4: CIT 40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of at least 2 on item 1 (depressed mood) • Depressive episode ≥ 4 wks • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies • Any DSM-IV Axis I disorder other than MDD • Score at least 5 on item 10 of MADRS	**Mean age (yrs):** D1: 40.1 D2: 40.7 D3: 39.6 D4: 40.0 **Sex (% female):** D1: 60 D2: 70 D3: 68 D4: 62 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.8 (5.9) D2: 24.3 (6.2) D3: 25.8 (5.7) D4: 25.9 (5.9)	**Sexual dysfunction (%):** D1: 0 D2: 9 D3: 12 D4: 4	NR	**Overall attrition rate:** 24% **Overall adverse events:** D1: 70.5 D2: 79 D3: 85.6 D4: 86.4 **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Chouinard et al., 1999[10] **Country and setting:** Canada Multicenter (8) **Funding:** SmithKline, Beecham	**Research objective:** To evaluate antidepressant and anxiolytic efficacy of PAR and FLUOX in patients with major depression **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 203 **Intervention:** D1: PAR: 20-50 mg/d D2: FLUOX: 20-80 mg/d	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 and score of 2 on HAM-D item 1 • Depression symptoms for at least 1 mo **Exclusion criteria:** • Pregnant or lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 2 mos • Suicidal tendencies	**Mean age (yrs):** D1: 40.6 D2: 41.2 **Sex (% female):** D1: 63.7 D2: 59.4 **Race (% white):** D1: 95.1 D2: 98.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.91 (0.46) D2: 25.45 (0.46)	**Sexual dysfunction:** D1: abnormal ejaculation: 24.3% of men, impotence/erectile dysfunction: 10.8% D2: abnormal ejaculation: 12.2% of men, impotence/erectile dysfunction: 7.3% of men	NR	**Overall attrition rate:** 36% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Clayton et al., 2002 [11] **Country and setting:** USA , Multicenter, primary care **Funding:** Glaxo Wellcome Inc.,	**Research objective:** To compare sexual functioning associated with newer antidepressants using a validated scale in patients with MDD **Duration of study:** **Study design:** observational/ cross-sectional **Overall study N:** 6000+ **Intervention:** D1: Bupropion IR , 255mg/d (mean dose) D2: Bupropion SR, 273.7mg/d (mean dose) D3: Citalopram, 24.9mg/d (mean dose) D4: Fluoxetine, 25.5mg/d (mean dose) D5: Paroxetine, 23.3mg/d (mean dose) D6: Sertraline, 81.4mg/d (mean dose) D7: Venlafaxine XR, 114.9mg/d (mean dose)	**Inclusion criteria:** • Aged at least 18 years • receiving monotherapy for depression (using one of the newer antidepressants: Bupropion IR/SR, Citalopram, Fluoxetine, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Venlafaxine or Venlafaxine XR • sexually active at some point during the prior 12 months **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications	**Target population:** **Mean age (yrs):** overall 30.2 **Sex (% female):** overall: 77.2 **Race (% white):** overall: 93.1 **Baseline (HAMD-24):** NR **Mean MADRS score at baseline:** NR	**Prevalence of SD (CSFQ-14), %** D1: NR D2: 7 D3: 30 D4: 23 (only graph shown, data not reported) D5: 25 (only graph shown, data not reported) D6: 25 (only graph shown, data not reported) D7: 30	CSFQ-14, gender-specific version	**Overall attrition rate:** NA **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Clayton et al., 2006[12] **Country and Setting** United States, multicenter **Funding** GlaxoSmithKline **Risk of Bias:** Fair	**Research objective** To compare effects on sexual functioning and antidepressant efficacy of once-daily BUP XL and ESC in adults with MDD. **Drugs, Doses, and Range** D1: BUP XL (150-450 mg 1 x daily): 150 mg 1x daily week 1 (low); 300 mg 1 x daily during weeks 2 to 4 (medium); on week 5, daily dose could be increased to 450 mg (high) if additional efficacy was desired D2: ESC (10-20 mg 1 x daily): 10 mg 1 x daily during weeks 1 to 4 (low); ESC dose could be increased to 20 mg 1 x daily (medium) for weeks 5 to 8 if additional efficacy was needed\ D3: PBO **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No	**Inclusion criteria:** • Adults (age range): ≥ 18 years • Diagnosed with MDD according to DSM-III or -IV • HAM-D: HAM-D-17 total score ≥ 19 at screening and on the day of randomization to treatment • Currently experiencing a MDE lasting ≥ 12 weeks and < 2 years, but were otherwise healthy • Normal orgasm function as assessed by investigator interview and were willing to discuss their sexual functioning with investigator and engaged in sexual activity leading to orgasm at least once every 2 weeks. Patients who had a sexual desire disorder were eligible for study if investigoator considered it to be secondary to MDE.	**Groups similar at baseline** Yes **n =** Pooled D1: 276 D2: 281 D3: 273 **Mean age, years** Pooled D1: 37 D2: 36 D3: 36 **Sex, % female** Pooled D1: 58 D2: 57 D3: 60 **Race, % white** Pooled D1: 70 D2: 68 D3: 70 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior**	D1: Orgasm Dysfunction: 15%; worsened sexual function: 20% D2: Orgasm Dysfunction: 30%; worsened sexual function: 36% D3: Orgasm Dysfunction: 9%; worsened sexual function: 15% **Withdrawals due to adverse events, %** Pooled: D1: 6 D2: 4 D3: 5 Study 1: D1: 3 D2: 5 D3: 5 Study 2: D1: 10 D2: 3 D3: 5 **Withdrawals due to lack of efficacy, %** D1: NR D2: NR D3: NR	CSFQ-14

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
	Study design RCT **Duration** 8 weeks **Type of depression** MDD **Intervention** BUP XL ESC PBO	**Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): A diagnosis of bipolar I or II disorder, schizophrenia, or other psychotic disorders • Suicidal tendencies (acute or other): history of attempted suicide within 6 months before screening. • Any sexual dysfunction at screening or at randomization except sexual desire disorder related to depression as determined by structured investigator interview • History or current diagnosis of anorexia nervosa, bulimia, seizure disorder, or brain injury • Diagnosis of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or acute stress disorder within 12 months before study entry **Outcome measures** • HAM-D: HAM-D-17 • CGI-S or CGI-I	**depressive episodes, %** D1: 100 D2: 100 D3: 100		

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		• CSFQ (secondary endpoint) • HAD			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Clayton et al., 2007[13] **Country and Setting** United States, multicenter (36 psychiatric clinical settings) **Funding** Eli Lilly and Company **Study Quality:** Good **Attrition rate, %:** 8 weeks: D1: 31.9 D2: 24.5 D3: 29.9 8 months: D1: 63.7 D2: 55.8 D3: 89.8* **Overall attrition, %:** Overall rate of attrition (8-months) = 65.8. rate of attrition for acute treatment phase (initial 8 weeks) = 28.5.	**Research objective** Comparisons of changes in sexual functioning for DUL and ESC in which primary objective was to compare onset of antidepressant action for DUL 60 mg/day with that of ESC 10 mg/day. secondary objection was to compare differential drug effects on sexual functioning over acute and longer-term course of study. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60 mg/day (medium) for initial eight-week acute-treatment phase; DUL 60-120 mg/day (medium-high) during extension phase D2: ESC (10-20 mg 1 x daily): 10 mg/day (low) for initial 8-week acute-treatment phase; 10-20 mg/day (low-high) during extension phase D3: PBO **Fixed dose** Yes **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT	**Inclusion criteria:** • Adults (age range): ≥ 18 years of age • Diagnosed with MDD according to DSM-III or -IV • MADRS: total score ≥ 22 • CGI-S: ≥ 4 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): Illicit drug and alcohol abuse: history of substance dependence within past 6 months • Clinically significant medical disease: Investigational drug use within last: A history of a lack of response, at any time, to an adequate trial of DUL (≥ 60 mg/day for ≥ 4 weeks), ESC (≥ 10 mg/day for ≥ 4 weeks), or CIT (≥ 20 mg/day for ≥ 4 weeks) • ECT or transcranial magnetic stimulation within past year • Suicidal tendencies (acute or other): serious suicidal risk • Any current primary	**Groups similar at baseline** Yes **n =** D1: 273 D2: 274 D3: 137 **Mean age, years** D1: 41.1 D2: 43.3 D3: 42.5 **Sex, % female** D1: 63.4 D2: 67.9 D3: 63.5 **Race, % white** D1: 75.5 D2: 77.4 D3: 82.5 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** The mean age of patients in DUL treatment group was significantly lower than that in ESC (41.1 years vs. 43.3 years; *P:* 0.036). CGI-S means	D1: incidence of treatment-emergent sexual dysfunction (acute phase, 8 weeks): 17/51 (33.3%); discontinuation due to SD Adverse Events, over 8 months: 2/273 erectile dysfunction (0.7% of total population, 2% of men) D2: incidence of treatment-emergent sexual dysfunction (acute phase, 8 weeks): 19/39 (48.7%); discontinuation due to SD Adverse Events, over 8 months: 7/274 (2.6%) **Overall adverse events, %:** NR At end point of acute-treatment phase (8 weeks or last observation), categorical assessment of changes in global sexual functioning in DUL-treated male patients showed that 54.4% reported improvement, 8.9% reported no change, and 36.7% reported worsening; whereas in ESC-treated male patients, 34.2% reported improvement, 6.6% reported no change, and 59.2% reported worsening (*P* = 0.019 DUL vs. ESC).	CSFQ-14

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
	Duration 8 months- included initial 8-week, acute-treatment phase + 24-week, double-blind, extension phase **Type of depression** MDD **Intervention** D1: DUL 60 mg QD D2: ESC 10 mg QD D3: PBO	Axis I disorder other than MDD • Any anxiety disorder as a primary diagnosis within past 6 months • Treatment-resistant depression • Current and primary Axis II disorder that could interefere with compliance with study protocol • Initiating, stopping, or changing psychotherapy during study • Treatment with MAOI within 14 days prior to visit 2; treatment with FLUOX within 30 days prior to visit 2. **Outcome measures** • HAM-D-17 • CSFQ	(SD) for treatment groups were reported at baseline. results are as follow: DUL 60 mg QD: 4.2 (0.7); ESC 10 mg QD: 4.2 (0.7); and PBO: 4.2 (0.7).	**Withdrawals due to adverse events, %** Sexual side effects at 8 months: D1: 0.7 D2: 2.6 D3: NR **Comments** Over 8-month course of study, withdrawal rates for sexual side effects did not differ for DUL (2/273) compared with ESC (7/274) (P = 0.07). Due to attrition and PBO rescue, number of PBO-treated patients significantly decreased after acute treatment.	

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Coleman et al., 1999[14] **Country and setting:** United States Multicenter (9 centers) **Funding:** Glaxo Wellcome Inc	**Research objective:** To compare sexual functioning as well as safety and efficacy of BUP SR and SER **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 240 **Intervention:** D1: SER: 50-200 mg/d D2: BUP: 150-400 mg/d D3: PBO	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Be in a stable relationship, have normal sexual functioning, and sexual activity at least once every 2 wks • Currently experiencing recurrent major episode of depression **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 38.3 D2: 38.1 D3: 38.5 **Sex (% female):** D1: 54 D2: 56 D3: 59 **Race (% white):** D1: 92 D2: 87 D3: 88 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 34.5 D2: 34.8 D3: 34.0	SD at 8 weeks: D1: Sexual Arousal Disorder: 9%; Orgasm Dysfunction: 36% D2: Sexual Arousal Disorder: 6%; Orgasm Dysfunction: 10%; total SD 16% D3: Sexual Arousal Disorder: 10%); Orgasm Dysfunction: 5%); total SD (excluding sexual desire disorder): 15%	structured clinical interview (only sexually active included); diagnosis based on DSM-IV criteria	**Overall attrition rate:** 30% **ITT Analysis** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Coleman et al., 2001[15] **Country and setting:** United States Multicenter (15 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of BUP, FLUOX and PBO on safety, efficacy and sexual functioning in patients with recurrent major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 456 **Intervention:** D1: FLUOX: 20-60 mg/d (26) D2: BUP: 150-400 mg/d (319) D3: PBO	**Inclusion criteria:** • Adults • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • Have sexual activity at least once every 2 wks • Currently experiencing episode lasting 2 to 24 mos • Currently in a stable relationship **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 37.1 D2: 36.6 D3: 36.7 **Sex (% female):** D1: 66 D2: 63 D3: 61 **Race (% white):** D1: 82 D2: 83 D3: 82 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 24.6 D2: 24.5 D3: 24.4	D1:orgasm dysfunction: overall 45/146 (30.8%) [34/104 (33% of those at usual dose), 11 (26% of those at high dose), 0 at low dose]; sexual arousal disorder (data only shown in graph), approx.): 12%; sexual desire disorder (data only shown in graph): 24% D2: overall 15/135 (11.1%) [15% (of those at usual dose), 12% of those at high dose, 0 at low dose]; sexual arousal disorder (data only shown in graph), approx.): (9/150) 6%; sexual desire disorder (data only shown in graph): (23/150)15% D3:18% Orgasm dysfunction occurred sig more in FLUOX patients compared with PBO or BUP SR patients ($P < 0.001$) At endpoint, more FLUOX treated patients had sexual	structured clinical interview (only sexually active included); diagnosis based on DSM-IV criteria (sexual function measured also at baseline; SD dichotomized as orgasm dysfunction, sexual desire disorder, and sexual arousal disorder)	**Overall attrition rate:** 34% **ITT Analysis** Yes **Study Quality:** Fair

				desire disorder than BUP SR treated patients ($P < 0.05$) Sig more buproion SR-treated patients were satisfied with sexual function (analysis only for patients satisfied at baseline; no data reported) $P < 0.05$ Compliance: 96.8% to 98.8% in all groups		

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Croft et al., 1999[16] **Country and setting:** United States Multicenter (8 centers) **Funding:** Glaxo Wellcome	**Research objective:** Comparison of efficacy and effects on sexual functioning of depressed patients using BUP, SER, or PBO **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 239 **Intervention:** D1: SER: 50-200 mg/d (mean = 121) D2: BUP: 150-400 mg/d (mean = 293)	**Inclusion criteria:** • Adults 18 and over • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • In stable relationship • Have normal sexual functioning and sexual activity at least once every 2 wks • Current depressive episode of 8 wks to 24 mos **Exclusion criteria:** • Pregnant	**Mean age (yrs):** D1: 36.0 D2: 35.9 D3: 37.4 **Sex (% female):** D1: 50 D2: 51 D3: 50 **Race (% white):** D1: 87 D2: 86 D3: 88 **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	SD day 56: D1: Sexual desire disorder: 28% (from baseline 43%); sexual arousal disorder: 6% (approx., data not reported, only shown in graph); orgasmic dysfunction (orgasm delay or failure); 41% (approx., data not reported, only shown in graph D2: Sexual desire disorder: 19% (from baseline 39%); sexual arousal disorder: 6% (approx., data not reported, only shown in graph); orgasmic	structured clinical interview, diagnosis according to DSM-IV definitions of SD; only sexually active & free of SD included	**Overall attrition rate:** 32% **ITT Analysis** Yes **Study Quality:** Fair

D3: PBO	• Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Suicidal tendencies	dysfunction (orgasm delay or failure): 15% (approx., data not reported, only shown in graph) D3: no data reported, only from graph: 10.5% (Sexual Arousal Disorder: 1.5%; Orgasm Dysfunction: 9%) both BUP and SER had higher sexual arousal disorder ($P < 0.05$) than PBO Orgasmic dysfunction occurred sig more in SER patients compared with PBO or BUP patients ($P < 0.001$)

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Cunningham et al., 1997[17] **Country and Setting** USA. Multicenter **Funding** Wyeth-Ayerst Research **Study Quality:** Fair **Attrition rate, %:** D1: 29% D2: 40% D3: 41% **Attrition Overall attrition,%:** 37 **Withdrawals due to lack of efficacy, %** D1: 2 D2: 4 D3:12	**Research objective** Comparison of the efficacy and safety of once-daily Venlafaxine extended release (XR) and immediate release versus placebo **Drugs, Doses, and Range** D1: Venlafaxine XR 75-150 mg D2: Venlafaxine IR 75-150 mg D3: Placebo **Fixed dose** **Flexible dose** yes **Dosages equivalent** yes **Study design** RCT (m-ITT) **Duration** 12 weeks **Type of depression** • MDD	**Inclusion criteria:** •Outpatients aged 18 years or older •*DSM-III-R* criteria for a major depressive episode; •minimum baseline score of 20 on HAM-D 21 •not more than a 20% decrease in score between screening and baseline; and had symptoms of depression for at least one month **Exclusion criteria**: • lactating or of childbearing potential with a positive pregnancy test • history of clinically significant medical disease or clinically significant abnormalities • acute suicidal tendencies; • History of a seizure disorder; presence of an organic mental disorder; bipolar disorder; or a history of any psychotic disorder not associated with depression • Any investigational drug, antipsychotic drug, or ECT within 30 days, fluoxetine within	**Groups similar at baseline - yes** **n =** D1: 92 D2: 87 D3: 99 **Mean age, years** D1: 39.7 D2: 42.8 D3: 39.7 **Sex, % female** D1: 63 D2: 67 D3: 59 **Race, % white** NR **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** **Comments:** NR	Abnormal ejaculation/orgasm (men) (%) D1: 27 (10/37) D2: 6 (2/31) D3: 0 (0/41) **Withdrawals due to adverse events, %** D1: 11 D2: 13 D3:2	spontaneously reported

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		21 days, or monoamine oxidase inhibitor,,paroxetine, or sertraline within 14 days, or use of any other antidepressant, anxiolytic, sedative-hypnotic drug, or psychotropic drug or substance within 7 days • any nonpsychotropic drug with psychotropic effects unless the dosage had been stable for a minimum of one month			

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Dalery and Honig 2003[18] **Country and setting:** Europe Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and FLUOX **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 184 **Intervention:** D1: FLUOX: 20 mg/d D2: FLUV: 100 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of ≥ 17 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 42.0 D2: 42.1 **Sex (% female):** D1: 63.3 D2: 62.7 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22.3 D2: 22.2	D1: ejaculatory dysfunction, erectile dysfunction: 2/35 (5.7% of men) D2: ejaculatory dysfunction 1/33 (3% of men)	NR	**Overall attrition rate:** 20.9% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)

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Author: Delgado et al., 2005[19] **Country and setting:** Country not reported, pooled analysis of 4 studies - setting not described in article **Funding:** Eli Lilly	**Research objective:** To assess sexual functioning in patients receiving DUL or PAR **Duration of study:** 8 wk acute phase followed by a 26 wk extension phase (for 2 of 4 studies) **Study design:** Pooled analysis of 4 RCTs **Overall study N:** 1,466 **Intervention:** D1: DUL: 40, 80, or 120 mg/d D2: PAR: 20 mg/d D3: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV **Exclusion criteria:** NR	**Mean age (yrs):** NR **Sex (% female):** NR **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	D1: acute phase (8 weeks); in the patients not meeting ASEX criteria for SD (DULOX n=241): treatment-emergent SD 46.4%; AE (no sex-specific data for denominator shown): discontinuation due to erectile dysfunction 1.2%; anorgasmia 0.1%; D2: treatment-emergent SD 61.4%, PAR (n=107); AE (no sex-specific data for denominator shown): discontinuation due to erectile dysfunction, PAR 0.8%; anorgasmia 0.1%, PAR 0.3% D3: treatment-emergent SD 28.8% ASEX (incidence of treat-emergent sexual dysfunction) sig higher for DUL vs. PBO DUL = 46.4% PBO = 28.8% t = 2.69, df = 1337, *P* = 0.007 PAR vs. PBO PAR = 61.4% PBO = 28.8% *P* < 0.001 DUL vs. PAR, *P* = 0.015 (incidence for DUL sig lower than incidence for PAR)	ASEX (SD outcomes measured in 475 patients who did not have sexual dysfunction at baseline); AE spontaneously reported	**Overall attrition rate:** NR **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Detke et al., 2002[20] **Country and setting:** United States, multicenter (18 sites) **Funding:** Eli Lilly and Company	**Research objective:** To evaluate efficacy of DUL vs. PBO for treatment of MDD and associated painful symptoms **Duration of study:** 9 wks **Study design:** RCT **Overall study N:** 245 **Intervention:** D1: DUL 60 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 or older • MDD according to DSM-IV • Minimum HAM-D-17 score of 15 • Other: CGI-S of 4 or more Note: Painful symptoms not required for inclusion **Exclusion criteria:** • Additional mental illness or organic mental disorder • Psychotherapy within 6 wks • Substance abuse or dependence (within 1 yr) • Clinically sig medical disease • Treatment resistant depression or lack of response of current MDD episode to 2 prior courses of therapy	**Mean age (yrs):** D1: 42.44 D2: 42.34 **Sex (% female):** D1: 65.0 D2: 68.0 **Race (% white):** D1: 87.0 D2: 84.4 **Baseline HAM-D-17:** D1: 21.42 (4.11) D2: 21.14 (3.72) **Baseline 100mm VAS (overall pain):** D1: 29.02 (25.10) D2: 28.16 (23.21) **Baseline HAM-A:** NR	**Discontinuation due to SD:** D1: 3/45 (6.7% of men) of DUL-treated men dropped out due to abnormal ejaculation	spontaneously reported	**Overall attrition rate:** NR **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Duration Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Detke et al., 2004[21] **Country and setting:** United States Multicenter, university clinics **Funding:** Eli Lilly	**Research objective:** To determine comparative efficacy and safety of DUL and PAR for treatment of MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 274 **Intervention:** D1: DUL 80 mg/d D2: DUL 120 mg/d D3: PAR: 20 mg/d D4: PBO	**Inclusion criteria:** • Adults 18 or older • Met DSM-IV and MINI criteria for MDD • CGI-S rating > 4 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 15 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 43.1 D2: 44.7 D3: 42.0 D4: 42.0 **Sex (% female):** D1: 70 D2: 70 D3: 58 D4: 58 **Race (% white):** D1: 95 D2: 92 D3: 86 D4: 86 **Baseline (HAM-A):** D1: 17.8 D2: 18.0 D3: 18.5 D4: 17.9 **Mean HAM-D score at baseline:** D1: 19.9 (3.6) D2: 20.2 (3.4) D3: 20.3 (4.1) D4: 19.9	treatment-emergent SD (ASEX): % D1: 46.5 D2: 46.5 D3: 62.8 D4: 40.5	ASEX	**Overall attrition rate:** 13.3% **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Duenas et al., 2011 [22] **Country and setting:** Multicenter, multiple countries, setting **Funding:** Eli Lilly and Co., Lilly Research Laboratories	**Research objective:** To compare long-term outcomes of duloxetine vs. SRI with respect to effectiveness, treatment-emergent sexual dysfunction (TESD) and QoL in patients with MDD **Duration of study:** 6 months **Study design:** observational, prospective **Overall study N:** 1647 **Intervention:** D1: SSRI combined (SSRI monotherapy: median dose (min, max): paroxetine: 20.0 (10.0, 480.0) mg/d, escitalopram: 10.0 (5.0, 100.0) mg/d, sertraline: 50.0 (20.0;400.0) mg/d, fluoxetine: 20.0 (10.0, 160.0) mg/d D2: Bupropion SR (300 mg/d)	**Inclusion criteria:** • Aged at least 18 years • sexually active during 2 weeks prior to study entry without sexual dysfunction • Diagnosed with MDD according to DSM-IV or ICD-10 with a CGI-S more than 4 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • any antidepresant medication prior 1 week to study (Fluoxetine: 1 month) • any current psychiatric disorder other than MDD as defined in DSM-IV, current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder, mental retardation, organic mental disorders or mental disorders due to a general medical condition,	**Groups similar at baseline:** partially not balanced **Mean age (yrs):** D1: 37.7 D2: 38.2 **Sex (% female):** D1: 58.3% D2: 51.8% **Race (% white):** D1: 18.1 D2: 23.7 **Baseline CGI-S score (mean)** D1: 4.5 D2: 4.5 **Mean MADRS score at baseline:** D1: 30.3 D2: 30.4	TESD, 6 month D1: physician reported) 28.7% in SSRI group (n=509); *patient-reported (TESD 6; ASEX)): approx. 36%* (data only shown in graph D2: TESD 6 (physician reported) 23.4% {OR 0.77; duloxetine vs. SSRI monotherapy) of TESD 6 (95% CI: 0.57; 1.04); P=0.087}; patient-reported: approx. 16% (data only shown in graph)	ASEX (physician- and patient-assessed)	**Overall attrition rate:** 23% **ITT analysis:** NA **Risk of Bias:** Moderate

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Ekselius et al., 1997[23] **Country and setting:** Sweden Multicenter (general physicians) **Funding:** Swedish Medical Research Council, Pfizer	**Research objective:** To compare efficacy and safety of SER with CIT in patients with major depression and examine occurrence and severity of sexual dysfunction symptoms beforea nd after 6 mos of treatment. **Duration of study:** 24 wks **Study design:** RCT (Completers analysis for sexual dysfunction) **Overall study N:** 400 **Intervention:** D1: SER: 50-100 mg/d D2: CIT: 20-60 mg/d	**Inclusion criteria:** • Adults 18 to 70 • Diagnosed with MDD according to DSM-III or -IV • MADRS at least 21 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Previous treatment with SER or CIT w/o sig effect	**Mean age (yrs):** D1: 47.0 D2: 47.2 **Sex (% female):** D1: 71 D2: 72.5 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	**Sexual dysfunction:** D1: AE, n : decreased sexual desire 7, erectile dysfunction (males): 2, ejaculatory dysfunction (males): 2 , orgasm dysfunction: 10; overall SD AE 27/200 (13.5%) D2: decreased sexual desire (at baseline): 46% of the women; 47% of the men; at the end of the study (week 24): 20% of the women, 24% of the men; AE, n: decreased sexual desire 13, erectile dysfunction (males): 3, ejaculatory dysfunction (males): 8, orgasm dysfunction: 14; overall SD AE 40/200 (20%) No statistically sig diffs between SER and CIT in magnitude or frequency of adverse sexual side effects Female patients reporting no sexual dysfunction at baseline, 11.8% reported decreased sexual desire and 14.3% reported	structured interview instrument (UKU Side Effect Scale) & AE spontaneous reporting	**Overall attrition rate:** 22% **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
				orgasmic dysfunction Male patients reporting no sexual dysfunction at baseline, 16.7% reported decreased sexual desire, 18.9% reported orgasmic dysfunction, 25% experienced ejaculatory dysfunction **Overall adverse events:** D1: 90 D2: 85.5		

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Fava et al., 1998[24] **Country and setting:** United States Multicenter (5 sites) **Funding:** SmithKline, Beecham	**Research objective:** Efficacy and tolerability of PAR and FLUOX **Duration of study:** 12 wks **Study design:** RCT **Overall study N:** 128 **Intervention:** D1: PAR: 20-50 mg/d (initial dosage of 20 mg/d could be increased wkly by 10 mg/d up to 50 mg/d) D2: FLUOX: 20-80 mg/d (initial dosage of 20 mg/d could be increased wkly by 20 mg/d up to 80 mg/d) D3: PBO	**Inclusion criteria:** • Minimum HAM-D score of 18 • Raskin Depression score of > 8 (and larger in value than Covi anxiety scale) **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • ECT within last 3 mos • Suicidal tendencies	**Mean age (yrs):** D1: 41.3 D2: 41.3 D3: 41.3 **Sex (% female):** D1: 50 D2: 50 D3: 50 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.1 (3.4) D2: 23.9 (3.8) D3: 23.7 (12.2)	**Sexual dysfunction (%):** D1: 25 D2: 7 D3: 0	spontaneously reported	**Overall attrition rate:** 28% **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Fava et al, 2002 [25] **Country and setting:** USA, Multicenter, psychiatry **Funding:** Lilly Research Laboratories, Eli Lilly and Company, US	**Research objective:** To analyze discontinuation-emergent adverse events comparing fluoxetine, sertraline, and paroxetine in patients with MDD and to test whether the presence of insomnia disorder is predictive of differential responsiveness or tolerability across SSRIs **Duration of study:** 10-16 wks **Study design:** RCT, double-blind **Overall study N:** 284 **Intervention:** D1: Fluoxetine, 20-60mg/d D2: Paroxetine, 20mg/d D3: Sertraline, 50-200mg/d	**Inclusion criteria:** • Aged at least 18 years • Diagnosed with MDD according to DSM-IV of at least 4-weeks' duration • Minimum baseline score of more than on the first 17 items (HAM-D-17) of the HAM-D-28. **Exclusion criteria:** • Pregnancy or breatfeeding • concomitant use of any antidepressant (other than study drugs), anxiolytic, other psychotropic medication within 7 days before study entry, with the exception of chloral hydrate; use of MAOIs within 2 weeks of active therapy or anticipated need to use an MAOI within 5 weeks of discontinuing the study • serious suicidal risk; • serious comorbid illness that was not stabilized; • presence of a seizure disorder	**Groups similar at baseline:** yes **Mean age (yrs):** D1: 42.1 D2: 42.5 D3: 44.0 **Sex (% female):** D1: 63.0 D2: 58.3 D3: 57.3 **Race (% white):** NR **Mean (HAM-D-17) score at baseline:** D1: 20.5 D2: 20.6 D3: 21.0	D1: 0 D2: 20% (abnormal ejaculation) D3: 0	open-ended question	**Overall attrition rate:** 29.6% **ITT analysis:** modified intent-to-treat set at least one post-baseline visit at which appropriate measurements were taken **Study Quality:** fair

	with a seizure occurring within the past year; • current or past history of organic mental disorder, substance-use disorder, schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, and antisocial personality disorder; mood-congruent or mood-incongruent psychotic features • known hypersensitivity to study medications	

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Feiger et al., 1996[26] **Country and setting:** Europe Multicenter (4) **Funding:** Bristol Myers Squibb	**Research objective:** To compare safety and efficacy of NEF with SER in outpatients with moderate to severe depression **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 160 **Intervention:** D1: NEF: 100-600 mg/d D2: SER: 50-200 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Illicit drug and alcohol abuse • Investigational drug use • Suicidal tendencies	**Mean age (yrs):** D1: 43 D2: 44.5 **Sex (% female):** D1: 48 D2: 55 **Race (% white):** D1: 90 D2: 79 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.5 D2: 23.5	Difficulty with ejaculation: D1: no sig AE on sexual function $P < 0.01$ D2: had sig AEs on sexual function D1: discontinuation due to SD side effects: n=0; comparison of scores from item responces are shown an differences calculated; since data from unvalidated questionnaire only, no estimation of SD possible D2: Erectile dysfunction: 7/45 (15.6% of men) **Overall adverse events:** D1: 96 D2: 95	unvalidated SD questionnaire, AE spontanceous reporting	**Overall attrition rate:** 24.4% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Feighner et al., 1991[27] **Country and setting:** United States Multicenter (2 sites) **Funding:** Burroughs Wellcome Co	**Research objective:** Efficacy and safety of BUP and FLUOX in depressed outpatients **Duration of study:** 6 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** D1: BUP: 225-450 mg/d (382) D2: FLUOX: 20-80 mg/d (38)	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 40.9 D2: 42.9 **Sex (% female):** D1: 62 D2: 61 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.3 D2: 26.1	D1: 0% D2: impotence/erectile dysfunction 4.7%, anorgasmia 1.7%, and libido decrease 1.7% (*P* = NR)	standardized open question to elicit AE	**Overall Attrition rate:** 7.3% **ITT Analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Ferguson et al., 2001[28] **Country and setting:** United States Multicenter (9 sites) **Funding:** Bristol Myers Squibb	**Research objective:** To compare effects of NEF and SER on reemergence rates of sexual dysfunction in depressed patients who'd had sexual dysfunction with previous SER treatment **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 75 **Intervention:** D1: NEF: 200-400 mg/d D2: SER: 50-100 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Receiving SER and experiencing attributable sexual dysfunction **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use within last 30 days	**Mean age (yrs):** D1: 43.2 D2: 44.8 **Sex (% female):** D1: 46 D2: 48 **Race (% white):** D1: 95 D2: 97 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 11.5 D2: 10.5	**Sexual dysfunctional (male ejaculation):** D1: 26% (10/39 D2: 76% (25/33) More SER treated patients had reemergence of sexual dysfunction than nefazadone-treated (76% vs. 26%; $P < 0.001$); **Overall adverse events:** D1: 100 D2: 97	Physicians Rating of Sexual Dysfunction Dymptoms (PRSDS), Rush-Presbytarian Sexual Function Inventory (R-SFI); AE spontaneously reported	**Overall attrition rate:** 32% **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Franchini et al., 1997[29] **Country and setting:** Italy Mood disorder clinic **Funding:** Not reported	**Research objective:** Efficacy and safety of fluvoxamine and sertraline in the long-term treatment of depression **Duration of study:** 24 months **Study design:** RCT **Overall study N:** 64 **Intervention:** D1: Sertraline: 100-200 mg/d D2: Fluvoxamine: 200-300 mg/d	**Inclusion criteria:** • Asymptomatic patients; unipolar patients with prior episodes; depressive episode within past 18 months; at least 4 months of remission confirmed by absence of symptoms according to DSM-IV; absence of other Axis I diagnosis **Exclusion criteria:** • Other Axis I diagnosis; low compliance with past treatments; mania or hypomania; prior long-term maintenance treatment; recurrence cycle not longer than 18 months	**Mean age (years):** Drug 1: 47.3 Drug 2: 49.0 **Sex (% female):** Drug 1: 78 Drug 2: 75 **Race (% white):** Drug 1: NR Drug 2: NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	**Sexual dysfunctional (male ejaculation):** D1: 4/7 (57.1% of men) D2: 0	NR	**Overall attrition rate:** NR **ITT Analysis** No, but not necessary since 100% completed trial with outcome assessments **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Gelenberg et al., 2003[30] **Country and setting:** United States Multiclinic **Funding:** Bristol-Myers-Squibb	**Research objective:** Comparison of NEF and PBO in prevention of depression recurrence **Duration of study:** 52 wks **Study design:** RCT **Overall study N:** 165 for maintenance phase **Intervention:** D1: NEF: 300-600 mg/d (495.2) D2: PBO D3: Overall	**Inclusion criteria:** • Adults 18 to 75 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 **Exclusion criteria:** • Pregnant • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 mos • Suicidial tendencies	**Mean age (yrs):** D1: 44.4 D2: 44.1 D3: 44.0 **Sex (% female):** D1: 69.7 D2: 65.5 D3: 67.5 **Race (% white):** Overall: 96.5 **Baseline HAM-A:** NR **Baseline HAM-D:** NR	**SD** D1: 2/78 (2.6%) D2: 3/87 (3.4%)	spontaneously reported	**Overall attrition rate:** 50.6% **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Gilaberte et al., 2001[31] **Country and setting:** Spain; multicenter (10) **Funding:** Eli Lilly and Co	**Research objective:** To evaluate efficacy and safety of FLUOX compared to PBO in maintenance treatment of recurrent unipolar depression **Duration of study:** 1 yr for maintenance (2 yrs total) **Study design:** RCT **Overall study N:** 140 (double-blind maintenance phase) **Intervention:** D1: FLUOX: 20-40 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • At least one prior depressive episode in last 5 yrs • CGI-S score at least 4 in index episode **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidial tendencies • Previous resistance to pharmacologic treatment	**Mean age (yrs):** D1: 44.4 D2: 43.8 **Sex (% female):** D1: 78.6 D2: 78.6 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 2.8 (2.0) D2: 3.1 (2.7)	D1: 9/70 (12.9%) D2: 10/70: 14.3% **Overall adverse events:** D1: 62.9 D2: 68.6	nonprobing inquiry	**Overall attrition rate:** 44.3% **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Golden et al., 2002[32] **Country and Setting** USA and Canada, multicenter **Funding** GlaxoSmithKline **Study Quality:** Fair (high attrition) **Is adherence reported?** NR **Rate of adherence or compliance** NR **Attrition** **Overall attrition, %:** 30.7 **Attrition rate, %:** D1: 25.7 D2: 31.3 D3: 26.3 **Withdrawals due to adverse events, %** D1: 10 D2: 16 D3: 6 **Withdrawals due**	**Research objective** To determine antidepressant efficacy and tolerability of PAR CR and PAR IR in adult patients with MDD. **Drugs, Doses, and Range** • PAR (10-60 mg 1 x daily): 20-50 mg/day (low to high) • PAR CR (12.5-75 mg 1 x daily): 25-62.5 mg/day (low to high) **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** Yes **Study design** RCT **Duration** 12 weeks **Type of depression** MDD **Intervention** D1: PAR CR D2: PAR IR D3: PBO	**Inclusion criteria:** • Adults (age range): 18-65 • Diagnosed with MDD according to DSM-III or -IV • HAM-D: 20 or more (and did not decrease by more than 25% between screening and baseline **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications: treatment with monoamine oxidase inhibitor, benzodiazepine, or other psychoactive agent (excluding chloral hydrate) • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse within 6 months of screening • ECT within last: 3 months • Suicidal tendencies (acute or other) • History of brief depressive episodes (≤8 weeks) • Homicidal risk	**Groups similar at baseline** Yes **n =** D1: 212 D2: 217 D3: 211 **Mean age, years** D1: 40.7 D2: 39.9 D3: 39.7 **Sex, % female** D1: 63.2 D2: 69.1 D3: 63.0 **Race, % white** D1: 88.2 D2: 86.6 D3: 85.3 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** **Outpatients/Inpatients** **Baseline mean HAM-A > 25?** NR	**Sexual dysfunction:** Abnormal ejaculation: D1: overall SD AE: 24/212 (11.3%) D2: at least 5% and 2x the rate of placebo-group; D3: 1 female,1 male: total SD 2/211 (0.095%)	non-leading question

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
to lack of efficacy, % NR **Comments** Dropout rate of patients with PAR IR sign. higher compared to PBO (*P* = 0.0008)		• Currently taking PAR or history of PAR nonresponse or intolerability **Outcome measures** • HAM-D: 17-item total score, depressed mood (item 1), psychic anxiety (item 10)	**Mean age at baseline** Less than 65 years **Mean HAM-D at baseline** Greater than 17 (moderate to severe)		

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Guelfi et al., 2001[33] **Country and setting:** France, Denmark, Belgium, Netherlands Multicenter (33) **Funding:** N.V. Organon, Oss, Netherlands	**Research objective:** To compare antidepressant efficacy and tolerability of MIR and VEN in treatment of hospitalized patients with DSM-IV diagnosis of severe depressive episode with melancholic features **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 157 **Intervention:** D1: MIR: 49.5 mg D2: VEN: 255.0 mg	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 25 • DSM-IV melancholic features **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Investigational drug use • ECT within last 3 mos • Suicidal tendencies • Current episode > 12 mos • > 2 previous episodes of major depression that did not respond to AD therapy	**Mean age (yrs):** D1: 45.9 D2: 44.5 **Sex (% female):** D1: 62.8 D2: 68.4 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 29.5 (3.0) D2: 29.2 (2.9)	D1: Orgasm dysfunction 9/78 (11.8%); Decreased sexual desire: 9/78 (11.8%) ; (29/49, males/females);3 ejaculatory overall SD: 21/78 (23.1%) D2: Orgasm dysfunction 9/79 (10.8%); Decreased sexual desire 11/79 (13.5%); (25/54 males/females); Ejaculatory dysfunction (males) 2/25 (9.1% of men); overall SD: 20/79 (25.3%) **Overall adverse events:** D1: 74.4 D2: 65.8	UKU side effects symptoms scale (UKU symptoms with an incidence of 10% in either treatment group, or a statistically significant difference between the groups)	**Overall attrition rate:** 29.3% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Hicks et al., 2002[34] **Country and setting:** UK Outpatient clinic **Funding:** Bristol Myers Squibb	**Research objective:** Compare NEF and PAR for treatment of depression and sleep in patients with mod-severe MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 40 **Intervention:** D1: NEF: 400-600 mg/d D2: PAR: 20-40 mg/d	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 30 days • Shift workers • Current sleep disorders	**Mean age (yrs):** D1: 42.75 D2: 42.95 **Sex (% female):** D1: 60 D2: 55 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 22 D2: 22.5	**Sexual dysfunction (%):** D1: 0 D2: 20	AE specifically monitored from checklist of symptoms	**Overall attrition rate:** 20% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Hochstrasser et al., 2001[35] **Country and setting:** Multinational, multicenter **Funding:** H. Lundbeck A/S	**Research objective:** To compare prophylactic efficacy of CIT vs. PBO in unipolar, recurrent depression following response to treatment with CIT in previous study periods **Duration of study:** 48-77 wks **Study design:** RCT **Overall study N:** (For period III): 269 **Intervention:** D1: CIT: 20, 40, or 60 mg (3 groups + PBO) D2: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 • Two or more previous depressive episodes (one within last 5 yrs) **Exclusion criteria:** • Pregnant • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • ECT within last 3 days to 8 wks • Suicidial tendencies • MADRS item 10 ≥ 5 • Current depressive episode longer than 6 mos • Family history of bipolar disorder	**Mean age (yrs):** D1: 43.8 (9.7) D2: 42.4 (11.5) **Sex (% female):** D1: 67.4 D2: 75 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** NR	D1: SD < 2.5% D2: 0%	open question	**Overall attrition rate:** NR **ITT Analysis** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Hypericum Depression Trial Study Group, 2002 [36] **Country and setting:** USA, Multicenter **Funding:** Study grants; study medications donated by Lichtwer Pharma and Pfizer;	**Research objective:** To test efficacy and safety of a well-characterized Hypericum perforatum extract (LI-160) against placebo and sertraline in patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 340 randomized **Intervention:** D1: PBO D2: SER: 50-100mg/d	**Inclusion criteria:** • Aged at least 18 years • Diagnosed with MDD according to DSM-IV • Minimum HAM-D total score of at least 20 at screening and baseline visits • Minimum Global Assessment of Functioning (GAF) total score of at least 20 **Exclusion criteria:** • score above 2 on the HAM-D suicide item, attempted suicied in teh last year; • pregnancy or planning pregnancy or breastfeeding; • liver disease or unstable serious disease • daily use of sertraline or Hypericum in the last 4 weeks prior to study entry; concomitant psychotheraputic or psychotropic medications, dietary supplements • any current	**Groups similar at baseline:** yes **Mean age (yrs):** D1: 40.1 D2: 43.9 **Sex (% female):** D1: 66.4 D2: 66.7 **Race (% white):** D1: 75.9 D2: 73.9 **Baseline (HAM-D-17):** D1: 22.7 D2: 22.5 **Mean GAF score at baseline:** D1: 54.1 D2: 53.6	D1: 13.8% D2: 32%	spontaneously reported or elicited (44-item checklist)	**Overall attrition rate:** 27.9% **ITT analysis:** modified ITT (excluding participants not fullfilling entry criteria (n=2) **Study Quality:** fair

	psychiatric disorder other than MDD as defined in DSM-IV, • current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder, mental retardation, organic mental disorders or mental disorders due to a general medical condition, any • substance abuse disorder within the previous 6 months, • known hypersensitivity to study medications	

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Katona et al., 2012 [37] **Country and setting:** Multicenter (Canada, Finland, France, Germany, Sweden, Ukraine and the USA), psychiatric, psychogeriatric and geriatric settings **Funding:** H. Lundbeck A/S, Takeda Pharmaceutical Company	**Research objective:** To compare efficacy, safety and tolerability of Lu AA21004 at 5 mg/day compared with placebo over 8 weeks in elderly patients with MDD with duloxetine (60mg/day) as an active reference **Duration of study:** 8 wks **Study design:** RCT, double-blind **Overall study N:** 296 **Intervention:** D1: PBO D2: DUL: 60mg/d	**Inclusion criteria:** • Aged at least 65 years • Diagnosed with MDD according to DSM-IV of at least 4-weeks' duration and with at least one previous MDE before the age of 60 years • Minimum MADRS total score of at least 26 at screening and baseline visits **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Mini-Mental State Examination (MMSE) score of less than 24 at screening • any current psychiatric disorder other than MDD as defined in DSM-IV, • current or past history of a manic or hypomanic episode, schizophrenia or any other psychotic disorder, mental retardation, organic mental disorders or mental disorders	**Groups similar at baseline:** yes **Mean age (yrs):** D1: 39 D2: 40 **Sex (% female):** D1: 70.3 D2: 70.9 **Race (% white):** D1: 95.9 D2: 95.4 **Baseline (HAMD-24):** D1: 29.4 D2: 28.5 **Mean MADRS score at baseline:** D1: 30.3 D2: 30.4	D1: 0 D2: 6 patients (male) 6/51 (11.8% of men): [abnormal orgasm and erectile dysfunction (1), decreased libido and erectile dysfunction (1), erectile dysfunction (1), delayed ejaculation (3)]	non-leading question to ascertain AE; no targeted questions/ no specific instrument used to assess SD	**Overall attrition rate:** 13.2% **ITT analysis:** modified intent-to-treat set – the full-analysis set (FAS), comprising all patients in the APTS who had at least one valid postbaseline assessment of the primary efficacy variable (HAM-D24 total score) **Risk of Bias:** low

	due to a general medical condition, any • substance abuse disorder within the previous 6 months, • presence or history of a clinically significant neurological • Suicidal tendencies • elevated intraocular pressure or at risk for acute narrow angle glaucoma, known hypersensitivity to duloxetine, a chronic liver disease, a clinically significant unstable illness	

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Keller et al., 1998[38] **Country and setting:** United States (10) outpatient psychiatric clinics and (2) academic centers **Funding:** Pfizer	**Research objective:** To determine if maintenance therapy with SER can effectively prevent recurrence of depression in patients with chronic major depression or double depression **Duration of study:** 76 wks **Study design:** RCT **Overall study N:** 161 **Intervention:** D1: SER: 50-200 mg/d D2: PBO	**Inclusion criteria:** • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • MDD with or without dysthymic disorder • Chronic depression defined as depression of at least 2 yrs duration • 3 phase study **Exclusion criteria:** NR	**Mean age (yrs):** D1: 40.8 D2: 42.4 **Sex (% female):** D1: 62 D2: 69 **Race (% white):** NR **Baseline HAM-A:** NR **Baseline HAM-D:** D1: 5.5 (4.2) D2: 6.3 (3.7)	**Sexual dysfunctional (male ejaculation):** D1: 13/77 (16.9%) D2: 0	NR	**Overall attrition rate:** 63.4% **ITT Analysis** No, time to event of full population **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Kiev and Feiger, 1997[39] **Country and setting:** United States Multicenter (2 centers) **Funding:** Solvay Pharmaceuticals, Upjohn	**Research objective:** To compare FLUV and PAR in treatment of outpatients with major depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 60 **Intervention:** D1: FLUV: 50-150 mg/d D2: PAR: 20-50 mg/d	**Inclusion criteria:** • Adults 18 to 65 • MDD diagnosis according to DSM-III or -IV • Minimum HAM-D score of 20; minimum score of 2 on “depressed mood” item **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies • Used a drug within 30 days with anticipated major organ toxicity • Participation in previous FLUV studies • Transportation difficulties	**Mean age (yrs):** D1: 42.7 D2: 39.9 **Sex (% female):** D1: 53 D2: 53 **Race (% white):** D1: 87 D2: 93 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 24.35 D2: 24.36	**Sexual dysfunction:** D1: ejaculation abnormality: 1/14 (7.1% of men); decreased libido: 4/30; total SD 5/30 (16.7%) D2: ejaculation abnormality: 3/14 (21.4% of men); decreased libido: 5/30 (16.7%); total SD: 8/30 (26.7%) **Overall adverse events:** D1: 97 D2: 100	observed or spontaneously/ reported AE	**Overall attrition rate:** 31% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Lepola et al., 2003[40] **Country and setting:** Europe and Canada Primary care **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy and tolerability of ESC compared to CIT and PBO in depression in primary care setting **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 315 **Intervention:** D1: CIT: 20-40 mg/d (mean 28.4) D2: ESC: 10-20 mg/d (mean 14.0) D3: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 22 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Suicidal tendencies	**Mean age (yrs):** D1: 43 D2: 43 D3: 43 **Sex (% female):** D1: 69.4 D2: 74.8 D3: 72.1 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	**Sexual dysfunction:** D1: 0 D2: 2/39 (5.6%) D3: 0 **Overall adverse events:** D1: 59.7 D2: 69.7 D3: 65	NR	**Overall attrition rate:** 7% **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author: Lineberry et al., 1990 [41] **Country and setting:** USA, multicenter **Funding:** Burroughs Wellcome & Co. **ITT** modified intent-to-treat set at least one post-baseline visit at which appropriate measurements were taken and at least one dose of medication **Overall rate of attrition, %** 26.0 **Study Quality:** Fair	**Research objective** To determine antidepressant efficacy and tolerability of Bupropion in lower daily dosages (300mg/d) in adult patients with MDD. **Intervention Drugs, Doses, and Range** D1: 300mg/day D2: PBO **Study design** RCT **n** 224 **Duration** 6 weeks **Type of depression** MDD	**Inclusion criteria** • Adults (age range): ≥ 18 years • DSM-III-R for current major depression • Be depressed for 4 weeks to 2 years • HAM-D total score at baseline at least 20 **Exclusion criteria** • Pregnancy or breatfeeding • concomitant use of any antidepressant (other than study drugs), anxiolytic, other psychotropic medication within 7 days before study entry; use of MAOIs within 2 weeks before study entry • previous treatment with bupropion • serious suicidal risk; • history of anorexia or bulimia • serious comorbid illness • preposition to seizures • substance abuse disorder withen the past 12 months to study entry	**Groups similar at baseline** Yes **n =** D1: 67 D2: 75 **Mean age, years (SD)** D1: 41.9 D2: 40.8 **Sex, % female** D1: 64.6 D2: 65.1 **Race (% white):** D1: 95.4 D2: 96.3 **Mean CGI-S score at baseline:** D1: 4.2 D2: 4.3	D1: impotence 2/39 (5.1% of men) D2: 0	standardized open question to elicit AE

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Mackay et al., 1999[42] **Country and setting:** UK General practice **Funding:** Reported as "many pharmacetical companies"	**Research objective:** To compare safety and side-effect profiles of NEFA, FLUOX, SER, VENLA and PAR in a cohort study **Duration of study:** N/A **Study design:** Cross sectional – prescription event monitoring **Overall study N:** 63,913 **Intervention:** D1: NEFA (n=11,834) D2: FLUOX (n=12,962) D3: SER (n=12,734) D4: PAR (n=13,741) D5: VENLA (n=12,642)	**Inclusion criteria:** • Patients prescribed SSRIs **Exclusion criteria:** None	**Survey Response rate:** 54.6% to 64.1% **Mean age (yrs):** D1: 45 D2: 50 D3: 49 D4: 49 D5: 48 **Sex (% female):** D1: 62.1 D2: 69.8 D3: 68.6 D4: 67.5 D5: 65.0 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	incidence density rate: number of AE/1000 patient months; men): D1: 0.8 D2: 0.2 D3: 0.7 D4: 2.5 D5: 1.5	AE monitoring questionnaire (not specified)	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Mehtonen et al., 2000[43] **Country and setting:** Scandinavia Multicenter **Funding:** Wyeth-Ayerst International	**Research objective:** Efficacy and safety of SER and VEN in outpatients with major depression **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 147 **Intervention:** D1: VEN: 75-150 mg/d D2: SER: 50-100 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Minimum HAM-D score of 18 **Exclusion criteria:** • Pregnant • Lactating • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease	**Mean age (yrs):** D1: 44.1 D2: 41.0 **Sex (% female):** D1: 65 D2: 67 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 25.5 (3.5) D2: 25.8 (4.5)	**Sexual dysfunction (including anorgasmia, impotence/erectile dysfunction, abnormal orgasm/ejaculation, increased/decreased libido):** D1: 6/75 (8%) D2: 4/72 (5.6%)	UKU side effect rating scale	**Overall attrition rate:** 19% **ITT analysis:** Yes **Study Quality:** Good

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Meijer et al., 2002[44] **Country and setting:** The Netherlands Multicenter (109 psychiatrists in general hospitals, regional institutes of mental health, or private practices) **Funding:** Pfizer, Inc	**Research objective:** To evaluate safety profile of SER vs. other SSRIs directly following introduction of SER to Dutch market **Duration of study:** 12 mo observation period **Study design:** Cohort study **Overall study N:** 1,251 **Intervention:** D1: SER D2: Other SSRIs (FLUOX FLUV PAR)	**Inclusion criteria:** • All patients with a new SER prescription; consecutive patients taking FLUOX, FLUV, or PAR used as controls **Exclusion criteria:** • No additional exclusion criteria were applied	**Mean age (yrs):** 41 (median) **Sex (% female):** 64.1% **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	**Sexual dysfunctional (male ejaculation):** D1: 2.1 D2: 3.7 D1: AE sexual dysfunction: N (incidence: number of first adverse events/1000 person-years): loss of libido 31 (0.27); ejaculation failure 14 (0.12), Impotence (male) 9 (0.08; other sexual function disorder (male) 4 (0.03); anorgasmia (female) 6 (0.05); other sexual function disorder (female) 3 (0.03); N (%) of sexual dysfunction AE %: male ejaculation: 5.7% of men (14/244: males denominator data: n=244); impotence 9/244 (3.7% of men); loss of libido 31/659 (4.7% of all); female anorgasmia 6/415 (1.4% of women); other sexual function disorder (female) 3/415 (0.07% of momen); **Overall adverse events:** D1: 73.4	open question	**Overall attrition rate:** N/A **ITT Analysis** N/A- observational study **Study Quality:** Fair

				D2: 75		

Study Characteristics	Research Objective Study Des	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Montejo et al., 2001[45] **Country and setting:** Spain Multicenter **Funding:** Bristol-Myers Squibb	**Research objective:** Incidence of sexual dysfunction associated with anti-depressant agents **Duration of study:** Carried out between April 1995 and February 2000 **Study design:** Prospective cohort study **Overall study N:** 1,022 **Intervention:** CIT FLUOX FLUV MIR NEF PAR SER VEN	**Inclusion criteria:** • Normal sexual functioning prior to taking antidepressants • Treatment with antidepressant alone or combine with benzodiazepine • Previous regular and satisfactory sexual practices • Occurrence of sexual dysfunction within 2 mos after introduction of antidepressant **Exclusion criteria:** • Prior sexual dysfunction • Combination of antidepressant and neuroleptic treatment • Treatment with hormones or any other drug capable of interfering with sexual intercourse • Sig intercurrent diseases affecting sexual function • Substance abuse	**Mean age (yrs):** Overall: 39.8 **Sex (% female):** Overall: 60 **Race (% white):** NR **Baseline (HAM-A):** NR **Baseline HAM-D:** NR	Overall incidence of sexual dysfunction was 59.1% Incidence of overall sexual dysfunction: FLUOX, 57.7% SER, 62.9% FLUV, 62.3% PAR, 70.7% CIT, 72.7% VEN, 67.3% MIR, 24.4% NEF, 8% Men had a higher frequency of sexual dysfunction (62.4%) than women (56.9%), although women had higher severity	Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ)	**Overall attrition rate:** N/A **ITT Analysis** Not applicable-observational study **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Montgomery et al., 2004[46] **Country and setting:** Mulitnational Primary care **Funding:** H. Lundbeck A/S	**Research objective:** To compare efficacy and tolerability of ESC to VEN XR in primary care patients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 297 **Intervention:** D1: ESC: 10-20 mg/d (12.1) D2: VEN: 75-150 mg/d (95.2)	**Inclusion criteria:** • Adults 18 to 85 • Diagnosed with MDD according to DSM-III or -IV • MADRS ≥ 18 **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Clinically sig medical disease • Suicidal tendencies	**Mean age (yrs):** D1: 49 D2: 47 **Sex (% female):** D1: 73 D2: 71 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 19.9 D2: 20.4	male impotence/erectile dysfunction (data only shown in bar chart, reported in Montgomery & Andersen, 2006) D1: 5.1% D2: 2.4%	AE spontaneously reported; Discontinuation Emergent Signs and Symptoms Checklist (DESS) checklist	**Overall attrition rate:** 14% **ITT analysis:** Yes **Study Quality:** Fair

Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder - Results from a Systematic Review with Network Meta-Analysis. *Drug Safety*; U. Reichenpfader, G. Gartlehner, L.C. Morgan, A. Greenblatt, B. Nussbaumer, R. A. Hansen, M. Van Noord, L. Lux, and B. N. Gaynes. **Corresponding author:** U. Reichenpfader, Department for Evidence-based Medicine and Clinical Epidemiology, Krems, Austria; Department of Medical and Health Sciences - Division of Community Medicine, Linköping University, Sweden; ureichenpfader@hotmail.com

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Moore et al., 2005[47] **Country and setting:** France Psychiatric and general practice **Funding:** H. Lundbeck A/S	**Research objective:** Efficacy of ESC vs. CIT in outpatients **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 294 (ITT = 280) **Intervention:** D1: ESC: 20 mg/d D2: CIT: 40 mg/d	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • MADRS of at least 30 **Exclusion criteria:** • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse	**Mean age (yrs):** D1: 44.1 D2: 46.2 **Sex (% female):** D1: 81.7 D2: 72 **Race (% white):** NR **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** NR	**Sexual dysfunction, %:** D1: 0 D2: 0.7 **Overall adverse events:** D1: 14.8 D2: 16.4	NR	**Overall attrition rate:** 7.5% **ITT analysis:** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Nemeroff et al., 1995[48] **Country and setting:** United States Multicenter **Funding:** Solvay Pharmaceuticals	**Research objective:** Comparison of efficacy and safety of FLUV and SER in treatment of depression **Duration of study:** 7 wks **Study design:** RCT **Overall study N:** 95 **Intervention:** D1: SER: 50-200 mg/d (137.1) D2: FLUV: 50-150 mg/d (123.8)	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 20 • HAM-D depressed mood item of at least 2 • Covi anxiety score less than Raskin score • Minimum score of 8 on Raskin Depression Scale **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Patients itolerant of SSRI side effects	**Mean age (yrs):** D1: 41.2 D2: 38.5 **Sex (% female):** D1: 60.9 D2: 61.2 **Race (% white):** D1: 84.8 D2: 98.0 **Baseline (HAM-A):** NR **Mean HAM-D score at baseline:** D1: 23.15 (2.77) D2: 24.57 (3.66)	**Sexual dysfunction, %:** D1: 28 D2: 10 **Overall adverse events:** D1: 93.5 D2: 85.7	specific question for AE, not described	**Overall attrition rate:** 28% **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Nierenberg et al, 2007 [49] **Country and Setting** 36 psychiatric clinical settings in U.S. **Funding** Eli Lilly **Overall attrition, %:** 27.9 **Attrition rate, %:** D1: 31 D2: 24 D3: 29 **Withdrawals due to lack of efficacy, %** D1: 3.3 D2: 1.5 D3: 5.1 **Study Quality:** Fair	**Research objective** To compare speed of onset of antidepressant efficacy for DUL and ESC. **Drugs, Doses, and Range** D1: DUL (40-60 mg 1-2 x daily): 60 mg QD; medium D2: ESC (10-20 mg 1 x daily): 10 mg QD; low D3: PBO **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **N** 684 **Duration** 8 weeks **Type of depression** MDD **Intervention** D1: DUL 60 mg QD D2: ESC 10 mg QD D3: PBO	**Inclusion criteria:** • Adults (age range): 18-79 • Diagnosed with MDD according to DSM-III or -IV • MADRS: ≥ 22 • CGIS: ≥ 4 **Exclusion criteria:** • Pregnant: HCG test at screening; Lactating; • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar): bipolar, schizo, Axis II disorder • Illicit drug and alcohol abuse: within last 6 mos. • Clinically significant medical disease • ECT within last: year • Suicidal tendencies (acute or other): decided by investigator • Other: anxiety within last 6 mos. **Outcome measures** • HAM-D: 20% decrease from baseline • CGI-S or CGI-I: 17% decrease from baseline	**Groups similar at baseline** Yes **n =** D1: 273 D2: 274 D3: 137 **Mean age, years** D1: 41.1 D2: 43.3 D3: 42.5 **Sex, % female** D1: 63.4 D2: 67.9 D3: 63.5 **Race, % white** D1: 75.5 D2: 77.4 D3: 82.5 **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	D1: AE: anorgasmia 4.4%; decreased libido 14/273 (5.1%) D2: erectile dysfunction 2/274 (0.7%); anorgasmia 10/274 (3.6%); decreased libido 11/274 (4%); overall SD: 23/274 (8.4%) D3: anorgasmia 0; decreased libido 3/137 (2.2%); overall: 2.2% **Overall adverse events, %:** D1: 85.7 D2: 81.0 D3: 78.1 **Withdrawals due to adverse events, %** D1: 7.3 D2: 5.1 D3: 5.8	spontaneously reported treatment-emergent AE

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		• HAM-A total score			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Perahia et al., 2006[50] **Country and Setting** Multinational, outpatient setting **Funding** Eli Lilly and Company; Boehringer Ingelheim **Attrition rate, %:** D1: 9 D2: 11 D3: 13 D4: 11 **Withdrawals due to adverse events, %** D1: 1 D2: 2 D3: 2 D4: 1 **Withdrawals due to lack of efficacy, %** D1: 4 D2: 3 D3: 2 D4: 1	**Research objective** To assess for efficacy and sefety of DUL doses of 80 and 120 mg/day in treatment of MDD. **Drugs, Doses, and Range** D1: DUL: 40 mg 2 x daily D2: DUL: 60 mg 2 x daily D3: PAR: 20 mg 1 x daily D4: PBO **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **N** 293 **Duration** 32 weeks **Type of depression** MDD	**Inclusion criteria:** • Adults (age range): at least 18 years • Diagnosed with MDD according to DSM-III or -IV • HAM-D: HAM-D total score greater than or equal to 15 • CGIS: greater than or equal to 4 **Exclusion criteria:** • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse • Clinically significant medical disease: cardiovascular, hepatic, renal, respiratory, hematological, endocrine, or neurological disease, or clinically significant laboratory abnormality • Investigational drug use within last • Suicidal tendencies	**Groups similar at baseline** Yes **n =** D1: 99 D2: 93 D3: 103 D4: 97 **Mean age, years** D1: 44.7 (10.1) D2: 46.5 (12.7) D3: 44.0 (10.8) D4: 45.8 (10.6) **Sex, % female** D1: 65.7 D2: 66.7 D3: 74.8 D4: 71.1 **Race, % white** 100 **Baseline HAM-A** D1: 18.8 (4.4) D2: 19.3 (4.9) D3: 19.5 (5.7) D4: 19.9 (5.1) **Insomnia, %** NR **Concomitant anergia, %** NR	**treatment–emergent dysfunction (ASEX) after 8 weeks (no baseline data shown):** D1: 63.1% D2: 30.1% D3: 64.1% D4: 9.6% Authors also utilized IRSD-F. Reports given were to validate Sex FX scale by examining correlations between Sex FX total and overall satisfaction scores and IRSD-F total score. A statistically significant negative correlation was found for both men and women between IRSD-F total and Sex FX scores reflecting inverse relation between function on Sex FX and dysfunction on IRSD-F. **Overall adverse events, %:** D1: 14.1 D2: 21.5 D3: 35.0 D4: 30.9	Spontaneously reported adverse events, ASEX: treatment–emergent dysfunction

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Study Quality: Fair		(acute or other) • Lack of response to at least two adequate courses of antidepressant therapy (at least 4 weeks' duration) within therapeutic dose range during their current MDD episode. **Outcome measures** • HAM-D: mean change from baseline in HAM-D 17 total score after 8 weeks of treatment • MADRS • CGI-S • PGI scale • SDS • VAS) for pain • SSI	**Experienced prior depressive episodes, %** NR		

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Rabkin et al., 2004[51] **Country and setting:** US Outpatient **Funding:** Lilly (provided tablets); Pharmacia and Upjohn (provided coded vials) National Institute of Mental Health	**Research objective:** To determine whether testosterone and FLUOX is superior to PBO for depression, fatigue, or both **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 123 **Intervention:** D1: FLUOX: 20-60 mg/d D2: PBO Testosterone 200-400 mg biwkly	**Inclusion criteria:** • Adults 18 or older • Diagnosed with MDD according to DSM-III or -IV • HIV seropositive • Dysthymia • Male • Negative PSA • Agreement of primary healthcare provider **Exclusion criteria:** • Additional mental illnesses or organic mental disorder • Illicit drug and alcohol abuse • Investigational drug use within last 5 wks • ECT • Suicidal tendencies • Psychotherapy started in last mo • Use of anabolic steroids • Current/anticipated change in ARV regimen within 4 wks • Unprotected intercourse with partners of unknown or negative HIV status	**Mean age (yrs):** D1: 40 D2: 41 **Sex (% female):** D1: 0 D2: 0 **Race (% white):** D1: 21.7 D2: 23.1 **Baseline (HAM-A):** NR **Baseline HAM-D:** D1: 18.2 (4.5) D2: 16.8 (3.3)	**Sexual dysfunctional (male ejaculation):** D1: 6 D2: 0	Structured Assessment of Treatment Emergent Events	**Overall attrition rate:** 26.8% **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias
Author: Reimherr et al.,1990 [52] **Country and setting:** USA, mulitcenter **Funding:** NR	**Research objective:** To compare efficacy, safety, and tolerance of sertraline against amitryptyline and placebo **Duration of study:** 8 weeks **Study design:** RCT, double-blind **Overall study N:** 448 **Intervention:** D1: SERTRALINE: 145mg D2: PBO	**Inclusion criteria:** • Adults 18 to 65 • Diagnosed with MDD according to DSM-III • Minimum HAM-D score of 18 on the first 18 items of the HAM-D • less than a 25% decrease in HAM_D score compared with screening value; higher score on the Raskin Depression Scale than on Covi Anxiety Scale **Exclusion criteria:** • Pregnant or breastfeeding • Concomitant psychotheraputic or psychotropic medications • Illicit drug and alcohol abuse • significant medical conditions • Suicidal tendencies • Schizophrenia or schizoaffective disorder	**Mean age (yrs), women:** D1: 40.0 D2: 40.2 **Mean age (yrs), men:** D1: 37.9 D2: 40.0 **Sex (% female):** D1: 53 D2: 52 **Race (% white):** D1: 91.3 D2: 92.7 **Baseline (HAM-D):** NR	D1: ejaculation disorder 15/70 (21.4% of men) D2: ejaculation disorder 1/72 (1.4% of men)	NR	**Overall attrition rate:** 39.2% **ITT Analysis** modified ITT (at least one efficacy assessment available and at lest one study dose medication) **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Rush et al., 1998 [53] **Country and setting:** USA, Canada, multicenter **Funding:** Bristol-Myers Squibb Pharmaceuticals; Sarah and Charles Seay Center for Research into the Biological Basis of Psychiatric Disorders, the University of Texas Southwestern Medical Center, NIMH	**Research objective:** To analyze the objective and subjective effects of nefazodone and fluoxetine on sleep as well as the timing of these effects over an 8-week, acute-phase treatment period in patients with MDD. **Duration of study:** 8 weeks **Study design:** RCT **Overall study N:** 125 **Intervention:** D1: Nefazodone, up to 200-500mg/d D2: Fluoxetine up to 40mg/d	**Inclusion criteria:** • Adults 19 to 55 • Diagnosed with MDD according to DSM-III-R • Minimum score of 18 on the first 17 items of the Hamilton Depression Rating Scale (HDRS-17) **Exclusion criteria:** • engaged in shiftwork; or had independent sleep/wake disorders identified on polysomnographs; • had documented significant concurrent general medical conditions; • met DSM-III-R criteria for psychoactive substance use disorder within the year prior to study. • Concomitant psychotheraputic or psychotropic medications • any other major lifetime DSM-III-R Axis I disorders (e.g., organic mental syndromes, bipolar, any	**Mean age (yrs):** D1: 46.0 D2: 37.0 **Sex (% female):** D1: 59 D2: 70 **Race (% white):** D1: 78 D2: 85 **Mean Baseline HAM-D-17 score:** D1: 22.9 D2: 23.3	D1: 0 D2: erectile dysfunction 2/18 (11%)	spontaneous reports	**Overall attrition rate:** 17% **ITT Analysis** modified ITT (all patients randomized to treatment, received a dose of study drug, and had at least one sleep or efficacy evaluation during treatment) **Study Quality:** Fair

	psychotic, any eating, panic, or obsessive–compulsive • pregnant, lactating, or sexually active women not using an adequate method of contraception.		

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Schatzberg & Roose, 2006[54] **Country and Setting** United States, Multicenter (21 university-affiliated and private research clinics) **Funding** Pharmaceutical company or other commercial source (please list name): Wyeth Research **Overall rate of attrition, %** 30% **Attrition rate, %** D1: 35.6 D2: 30 D3: 4 **Withdrawals due to adverse events, %** D1: 27 D2: 19 D3: 9.4 **Attrition due to lack of efficacy, %** NR **Overall adverse**	**Research objective** To compare efficacy of VEN IR and FLUOX with PBO in a sample of patients over age of 65 with depression. **Intervention Drugs, Doses, and Range** D1: VEN 37.5-225 mg/day (low - high) D2: FLUOX 20-60 mg/day low -high) D3: PBO **Study design** RCT **n** 300 **Duration** 8 weeks **Type of depression** Major depressive disorder unipolar depression (single or recurrent, nonpsychotic)	**Inclusion criteria** • Adults (age range): 65 years and older • HAM-D: 21-item HAM-D score ≥ 20 at initial visit • Not living in a residential setting • Unipolar (single or recurrent, nonpsychotic), with a current episode of at least 4 weeks in duration **Exclusion criteria** • Concomitant psychotheraputic or psychotropic medications: within prior 30 days • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) • Illicit drug and alcohol abuse within past year • Clinically significant medical disease • Investigational drug use within last: 30 days • ECT within last: 3 months • Suicidal tendencies (acute or other) • MMSE score = < 18 • FLUOX or VEN in past six months • Astemizole, cisapride,	**Groups similar at baseline** Yes **n =** D1: 104 D2: 100 D3: 96 **Mean age, years** D1: 71 D2: 71 D3: 71 **Sex, % female** D1: 56 D2: 45 D3: 46 **Race, % white** D1: 93 D2: 93 D3: 93 **Baseline HAM-A** NR **Insomnia, %:** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR	**Sexual dysfunction, %:** D1: 8.8 D2: 8 D3: 1.0	NR

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
events, %: D1: 26 D2: 19 D3: 9.4 **Risk of Bias** Fair		sumatriptan, terfenadine, PAR, SER, or any monoamine oxidase inhibitor within 14 days • Used any other antidepressant, anxiolytic, or sedative-hypnotic durg (except choloral hydrate) • Known hypersensitivity to VEN or FLUOX			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Segraves et al., 2000[55] **Country and setting:** United States Multicenter **Funding:** Glaxo Wellcome, Inc	**Research objective:** To compare efficacy and safety of BUP SR and SER, and to determine whether baseline anxiety predicts antidepressant response **Duration of study:** 16 wks **Study design:** RCT **Overall study N:** 248 **Intervention:** D1: BUP: 100-300 mg/d (mean 238 mg/d) D2: SER: 50-200 mg/d (mean 114 mg/d)	**Inclusion criteria:** • Adults 18 to 76 • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of 18 • Stable relationship with normal sexual functioning **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Additional mental illnesses or organic mental disorder • Suicidal tendencies • History/current diagnosis of eating disorders • Known predisposition to seizures	**Mean age (yrs):** D1: 39 D2: 40 **Sex (% female):** D1: 48 D2: 48 **Race (% white):** D1: 93 D2: 94 **Baseline (HAM-A):** D1: 16.6 (5.2) D2: 16.6 (5.2) **Mean HAM-D score at baseline:** D1: 24.8 (4.6) D2: 24.8 (4.6)	D1: overall % of sexual desire disorder (baseline): 54%, at the end of the treatment phase: 21%; sexual dysfunction combined (sexual arousal disorder, orgasm dysfunction, or premature ejaculation): men 15%; women: 7%; D2: overall % of sexual desire disorder (treatment-emergent) 26%, at the end of the treatment phase: sexual dysfunction combined (sexual arousal disorder:16%, orgasm dysfunction: 52%, or premature ejaculation): men 63%; women: 41%: 66/126 (52.4%)	standardized screening for SD, not specified; patient satisfaction with overall sexual functioning using a 6-point, Likert-scale; coding of SD using DSM-IV	**Overall attrition rate:** 31.5% **ITT analysis:** Yes **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Shelton, 2006[56] **Country and Setting** Eight U.S. sites (type not reported) **Funding** Pfizer, Inc. **Attrition Overall attrition, %:** 20 **Attrition rate, %:** D1: 23 D2: 17 **Withdrawals due to adverse events, %** D1: 1 D2: 4 **Withdrawals due to lack of efficacy, %** D1: NR D2: NR **Study Quality:** Fair	**Research objective** To compare efficacy, safety, and tolerability of SER and VEN XR in outpatients with MDD. **Drugs, Doses, and Range** D1: SER (25-200 mg 1 x daily): 50-150mg QD; Low-Medium; Maximum dose as tolerated. D2: VEN XR (75-225 mg 1 x daily): 75-225 mg QD; Low-High; Maximum dose as tolerated. **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **N** 160 **Duration** 8 weeks **Type of depression** MDD **Intervention** SER VEN XR	**Inclusion criteria:** • Adults aged 18+ • Diagnosed with MDD according to DSM-III or -IV: • Single episode or recurrent w/o psychotic features. • HAM-D: ≥ 18 on HAM-D17 and ≥ 2 on item 1 (depressed mood). **Exclusion criteria:** • Pregnant: Positive pregnancy test excluded participant. • Lactating: Concomitant psychotheraputic or psychotropic medications • Use of an antidepressant within 2 weeks of baseline (4 weeks for FLUOX) • Use of any psychotropics within 1 week of baseline (except zolpidem or zopiclone) • Use of benzodiazepines taken on a regular, daily basis within 4 weeks of baseline • Monoamine oxidase inhibitors within 14 days of baseline evaluation. • Additional mental illnesses or organic mental disorder not	**Groups similar at baseline** Yes **n =** D1: 82 D2: 78 **Mean age, years (SD)** D1: 41.2 (12.0) D2: 37.2 (11.6) **Sex, % female** D1: 46 D2: 61 **Race, % white** D1: 83 D2: 84 **Baseline HAM-A (SD)** D1: 15.7 (5.1) D2: 16.0 (4.4) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 51 D2: 52 **Comments:** NR	**Sexual dysfunction:** D1: 15/82 (18.3%) D2: 16/78 (20.5%) **Overall adverse events, %:** D1: 80 D2: 79	spontaneously reported by patient or recorded by investigator Treatment Emergent Symptom Scale)

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		related to depression (e.g., schizophrenia, bipolar) • Current or past diagnosis of bipolar disorder or any psychotic disorder • Current diagnosis of delirium or dementia • A mental condition rendering patient unable to understand study • Schizoid, schizotypal, or borderline personality disorder. • Illicit drug and alcohol abuse • Alcohol or Ddependence or abuse within last 6 months. • Clinically significant medical disease • Any serious and/or unstable medical condition • Abnormal baseline laboratory finding considered indicative of conditions that might affect study results • Impaired hepatic function • Impaired renal function • History of seizure disorder. • Investigational drug use within last: 90 days • ECT within last: 30 days			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		• Suicidal tendencies (acute or other): Score of 3 or 4 on suicide item of HAMD. • Previous non-response to SER, VEN XR, or to 2 antidepressants in current episode • Use of herbal and/or homeopathic remedies within 2 weeks of baseline • History of intolerance or hypersensitivity to SER and/or VEN XR • Likelihood of requiring treatment during study period with drugs not permitted by study protocol. **Outcome measures** • HAM-D • CGI-S and CGI-I • QOL scales: Q-LES-Q • HAM-A			

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Simon et. al., 2004[57] **Country and setting:** United States Multicenter study **Funding:** Wyeth	**Research objective:** To evaluate efficacy of VEN XR in prevention of relapse of depression by continuation treatment **Duration of study:** 8 wk acute phase; 6 mo continuation phase **Study design:** RCT **Overall study N:** 318 entered relapse prevention study (490 in acute phase) **Intervention:** D1: VEN XR 75-225 mg/d D2: PBO	**Inclusion criteria:** • Adults 18+ • Diagnosed with MDD according to DSM-III or -IV • Minimum HAM-D score of >20 • No greater than 20% decrease in HAM D between evaluations **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Clinically sig medical disease • Investigational drug use • Suicidial tendencies • Seizure • Antipsychotic medication • FLUOX within 30 days	**Mean age (yrs):** D1: 43 D2: 41 **Sex (% female):** D1: 102 (66%) D2: 86 (62%) **Race (% white):** NR **Baseline HAM-A:** N/A **Baseline HAM-D:** D1: 6.5 D2: 6.4	**Sexual dysfunction:** D1: abnormal ejaculation 5.3% of men D2: abnormal ejaculation 1.9% of men **Overall adverse events:** D1: 97% D2: 93%	NR	**Overall attrition rate:** 62% **ITT Analysis** Yes **Study Quality:** Fair

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Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Thase et al., 1997 [58] **Country and setting:** United States Multicenter **Funding:** Wyeth Ayerst Research	**Research objective:** To evaluate efficacy and tolerability of VEN XR once daily in outpatients with MDD **Duration of study:** 8 wks **Study design:** RCT **Overall study N:** 197 **Intervention:** D1: VENLAFAXINE XR: 75-225 mg/d D2: PBO	**Inclusion criteria:** • Adults 18 and older • Diagnosed with MDD according to DSM-IV with duration of at least a month • Minimum HAM-D score of 20 on the HAM-D-21 and less than a 20% decrease in HAM-D score compared with screening value; **Exclusion criteria:** • Pregnant or breastfeeding • antipsychotic medications or ECT within 30 days prior to study entry • fluoxetine within 21 days prior to study entry or MAOs within 14 days prior to study entry • Illicit drug and alcohol abuse • significant medical conditions • acute suicidal tendencies • history of seizures • history oof bipolar or psychotic disorder	**Mean age (yrs):** D1: 40 D2: 42 **Sex (% female):** D1: 60 D2: 61 **Race (% white):** NR **Mean HAM-D-21 score at baseline:** D1: 25 D2: 24 **Mean MADRS score at baseline:** D1: 28 D2: 28	D1: abnormal ejaculation/orgasm: men: 8/35 (22.9% of men); women: 2/60 (3.3% of women); impotence 5/35; female anorgasmia 4/60; SD AE: overall: 19/95 (20%) D2: 2/102 (2%)	spontaneously reported	**Overall attrition rate:** 34% **ITT analysis:** modified ITT (at least received one dose of study medication and one efficacy assessment) **Study Quality:** Fair

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Trivedi et al, 2004 [59] **Country and setting:** USA, Multicenter (academic and community centers) **Funding:** GlaxoSmithKline Pharmaceuticals	**Research objective:** To evaluate efficacy and tolerability of lower doses of paroxetine CR in patients with MDD **Duration of study:** 8 wks **Study design:** RCT, double-blind **Overall study N:** 459 **Intervention:** D1: PBO D2: Paroxetine CR 12.5mg/d D3: Paroxetine CR 25mg/d	**Inclusion criteria:** • Adults 18 and older • Diagnosed with MDD according to DSM-IV with duration of at least a month • Minimum HAM-D score of 20 on the HAM-D-17 and a score of more than 2 on item 2 on HAM-D at both screening and baseline visit **Exclusion criteria:** • any current psychiatric disorder other than MDD • Concomitant psychotheraputic or psychotropic medications • lifetime history of a manic or hypomanic episode, schizophrenia , schozoaffective disorder or bipolar disorder • general medical condition, any • substance abuse disorder within the previous 3 months, • substance dependence within the previous 6 months	**Groups similar at baseline:** yes **Mean age (yrs):** D1: 38.4 D2: 38.6 D3: 39.4 **Sex (% female):** D1: 61.6 D2: 54.2 D3: 59.5 **Race (% white):** D1: 74.0 D2: 76.5 D3: 76.4 **Mean (HAMD-27) score at baseline:** D1: 23.8 D2: 23.2 D3: 23.5 **Mean CGI-S score at baseline:** D1: 3.0 D2: 3.0 D3: 3.0	D1: men & women, decrease2 libido: 6/146 (4.2%) D2: men & women, decreased libido: 12/156 (7.7%); ejaculation disorder: 4/70 (5.7% of men); D3: men & women, decreased libido: 4/154 (2.6%); ejaculation disorder: 6/70 (8.6% of men)	patients questioned at each visit to report AE	**Overall attrition rate:** 23.7% **ITT analysis:** modified intent-to-treat set comprising all patients who had at least one valid postbaseline assessment of the primary efficacy variable and received at least one dose of study medication **Study Quality:** fair

	• presence or history of a clinically significant neurological • Suicidal tendencies • lifetime history of seizures • ECT within pevious 3 months • use of study medication within previous 12 months	

Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder - Results from a Systematic Review with Network Meta-Analysis. *Drug Safety*; U. Reichenpfader, G. Gartlehner, L.C. Morgan, A. Greenblatt, B. Nussbaumer, R. A. Hansen, M. Van Noord, L. Lux, and B. N. Gaynes. **Corresponding author:** U. Reichenpfader, Department for Evidence-based Medicine and Clinical Epidemiology, Krems, Austria; Department of Medical and Health Sciences - Division of Community Medicine, Linköping University, Sweden; ureichenpfader@hotmail.com

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Ventura et al, 2007[60] **Country and Setting** multicenter (8 Centers). United States **Funding** Forest Laboratories **Attrition** **Overall attrition, %:** 16% **Attrition rate, %:** D1: 17% D2: 14% **Withdrawals due to adverse events, %** D1: 2 D2: 4 **Withdrawals due to lack of efficacy, %** D1: 0 D2: 0 **Study Quality:** Fair .	**Research objective** Comparison of efficacy and tolerability of a fixed dose of ESC with SER **Drugs, Doses, and Range** D1: ESC (10-20 mg 1 x daily): 10 mg QD; Low D2: SER (25-200 mg 1 x daily): 50-200 mg QD; Low, Medium, or High **Fixed dose** No **Flexible dose** Yes **Dosages equivalent** No **Study design** RCT **N** 215 **Duration** 8 week + 1 week lead-in **Type of depression** MDD **Intervention** ESC SER	**Inclusion criteria:** • Adults (age range): 18-80 • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • MADRS: ¡Ý22 at both screening and baseline • CGIS: Concomitant condition (e.g., alcoholism, anxiety, stroke) **Exclusion criteria:** • Pregnant • Negative pregnancy test • Women of childbearing potential not on accepted form of contraception • Lactating • Concomitant psychotheraputic or psychotropic medications • Use of a depot neruoleptic within 6 months. • Use of any neuroleptic, antidepressant, or anxiolytic medication within 2 week (5 weeks for FLUOX). • Treatment with either ESCalopam or SER. • Failure to respond to adequate trials of any two SSRIs. • Any psychotropic	**Groups similar at baseline** Yes **n =** D1: 107 D2: 108 **Mean age, years** D1: 40.6 D2: 38.1 **Sex, % female** D1: 54.8% D2: 60.2% **Race, % white** D1: 82.7% D2: 89.8% **Baseline HAM-A** D1: 15.9 (0.5 SE) D2: 15.6 (0.5 SE) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Use of sleep medication, % D1: 9.6 D2: 7.4	**Sexual dysfunction:** D1: Ejaculation disorder: 11/47 (23.4% of men); Libido decreased: 10/107 (9.3% D2: Ejaculation disorder: 10/43 (23.3%); Libido decreased: 15/108 (13.9%) **Overall adverse events, %:** D1: 49% D2: 62%	spontaneously reported

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		Dexcept zaleplon or zolpidem for sleep. • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia, bipolar) Following were all listed as exclusion criteria: • Primary Axis I disorder other than MDD • history of any DSM-IV defined psychotic disorder • DSM-IV criteria for bipolar disorder, schizophrenia, obsessive-compulsive disorder, mental retardation, or pervasive development disorder. • Current psychotic disorder, personality disorder of sufficient severity to interfere with participation. • Illicit drug and alcohol abuse: Dependency as defined by DSM-IV. • Clinically significant medical disease • Findings from physical examination, laboratory test, and ECG were required to be normal or clinically insignificant. • Investigational drug use within last month.			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		• Suicidal tendencies (acute or other) **Outcome measures** • HAM-D: HAMD baseline; HAMD anxiety subscale • MADRS • CGI-S and CGI-I • Quality of life scales: Quality of Life Enjoyment and Satisfaction Questionnaire • Others: HAM-A; CES-D			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion	Baseline Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD	Analysis and Study Quality (Risk of Bias)
Author: Wade et al., 2002 [61] **Country and setting:** Multicenter (Canada, Estonia, France, the Netherlands and the UK), primary care **Funding:** H. Lundbeck A/S,	**Research objective:** To compare efficacy, safety and tolerability of escitalopram at a fixed dose of 10 mg/ day was compared with that of placebo in patients with MDD in a primary care setting **Duration of study:** 8 wks **Study design:** RCT, double-blind **Overall study N:** 300 **Intervention:** D1: PBO D2: ESC: 10 mg/d	**Inclusion criteria:** • Age 18- 65 years • Diagnosed with MDD according to DSM-IV • MADRS total scores ≥ 22 and ≤40 at screening and baseline visits **Exclusion criteria:** • mania or any bipolar disorder, schizophrenia or any psychotic disorder, obsessive–compulsive disorder, eating disorders, mental retardation, any pervasive developmental disorder or cognitive disorder (according to DSM-IV criteria • Concomitant psychotheraputic or psychotropic medications (antipsychotics, antidepressants, hypnotics, anxiolytics (except benzodiazepines or insomnia), antiepileptics, barbiturates, chloral hydrate or other 5-HT receptor	**Groups similar at baseline:** yes **Mean age (yrs):** D1: 40 D2: 41 **Sex (% female):** D1: 77.8 D2: 73.8 **Race (% white):** overal >97% **Baseline MADRS 22-29 (moderately ill):** D1: 59.8 D2: 57.4 **Baseline MADRS 30-40 (severely ill):** D1: 40.2 D2: 42.6	D1: 0 D2: 3/50 (6% of men)	NR	**Overall attrition rate:** 16% **ITT analysis:** modified ITT (included all randomized patients who took at least one dose of double-blind study medication and who had at least one post-baseline assessment of MADRS total score) **Study Quality:** Fair

	agonists • MADRS score $\geq$ 5 on item 10 (suicidal thoughts) • ECT, treatment with behaviour therapy or psychotherapy	

Sexual Dysfunction associated with Second-Generation Antidepressants in Patients with Major Depressive Disorder - Results from a Systematic Review with Network Meta-Analysis. *Drug Safety*; U. Reichenpfader, G. Gartlehner, L.C. Morgan, A. Greenblatt, B. Nussbaumer, R. A. Hansen, M. Van Noord, L. Lux, and B. N. Gaynes. **Corresponding author:** U. Reichenpfader, Department for Evidence-based Medicine and Clinical Epidemiology, Krems, Austria; Department of Medical and Health Sciences - Division of Community Medicine, Linköping University, Sweden; ureichenpfader@hotmail.com

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Wade et al., 2007[62] **Country and Setting** Multinational, Multicenters (psychiatric outpatient and general practice settings) **Funding** H. Lundbeck A/S **Attrition** **Overall attrition, %:** 23% **Attrition rate, %:** D1: 22.2 D2: 24.5 **Withdrawals due to adverse events, %** D1: 9.0 D2: 17.2 **Withdrawals due to lack of efficacy, %** D1: 4.9 D2: 1.3 **Study Quality:** Fair	**Research objective** The objective was to examine efficacy and tolerability of ESC compared to DUL in patients with moderate to severe MDD patients over 24 weeks, with a secondary enpoint at 8 weeks. **Drugs, Doses, and Range** D1: ESC 20 mg/day (Primary Analysis- endpoint at 24 weeks) D2: DUL 60 mg/day (Primary Analysis- endpoint at 24 weeks) **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** No **Study design** RCT **Duration** 24 weeks **Type of depression** MDD **Intervention** ESC 20 mg/day DUL 60 mg/day	**Inclusion criteria:** • Adults (age range): 18 - 65 years of age • Diagnosed with MDD according to DSM-III or -IV • MADRS: total score greater than or equal to 26 • CGIS: greater than or equal to 4 • Other: Patients with a secondary current comorbid anxiety disorder could be included, except obsessive-compulsive disorder, post traumatic stress disorder, or panic disorder **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications: (except zolpidem, zolpiclone and zaleplon used episodically for insomnia) within 2 weeks prior to baseline or during study • Additional mental illnesses or organic mental disorder not related to depression (e.g., schizophrenia,	**Groups similar at baseline** Yes **n =** D1: 141 D2: 146 **Mean age, years** D1: 43.3 (11.6) D2: 44.5 (11.0) **Sex, % female** D1: 74.1 D2: 70.2 **Race, % white** D1: 94.4 D2: 97.4 **Baseline HAM-A** D1: 22.1 (7.6) D2: 21.9 (6.5) **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** NR **Comments:** Base on intent-to-treat population (ESC, n = 141, DUL, n = 146)	**Sexual dysfunction** (including anorgasmia, ejaculation failure, erectile dysfunction, ejaculation delayed, orgasm abnormal, ejaculation disorder, libido decrease and loss of libido): D1: 7/144 (4.9%) D2: 10/151 (6.6%) **Overall adverse events, %:** D1: 77.6 D2: 74.8	reported spontaneously by the patients or in response to a non-leading question by the investigator

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		bipolar): bipolar disorder, psychotic disorder or features, current eating disorders (anorexia nervosa, bulimia), mental retardation, any pervasive developmental disorder or cognitive disorder • Illicit drug and alcohol abuse within 12 months prior to baseline • ECT within last 6 months • Suicidal tendencies • Receiving formal, behaviour therapy or systematic psychotherapy • History of lactose intolerance, hypersensitivity or non-response to CIT, or ESC, or DUL, or with increased intra-ocular pressure, or at risk of acute narrow-angle glaucoma **Outcome measures** • HAM-D • MADRS: adjusted mean change in MADRS total score from baseline to 24 weeks • CGI-S or CGI-I • Quality of life scales: MOS 36 - Item Health Survey (SF-36)			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		• Others: HAM-A, Sheehan Disability Scale (SDS)			

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
Author, Year Yevtushenko et al., 2007[63] **Country and Setting** Eight psychiatric out-patient clinics across Federation of Russia **Funding** OOO ARBACOM (Russian pharmaceutical company) **Attrition** **Overall attrition, %:** 2.40% **Attrition rate, %:** D1: 1% D2: 5% D3: 2% **Overall adverse events,%:** D1: 6.5 D2: 15.1 D3: 17.6 **Withdrawals due**	**Research objective** To compare efficacy and tolerability of ESC and CIT in outpatients with MDD (MDD). **Drugs, Doses, and Range** D1: CIT: 10 mg/d D2: CIT 20 mg/d D3: ESC: 10 mg/d **Fixed dose** Yes **Flexible dose** No **Dosages equivalent** Yes **Study design** RCT **Duration** 6 weeks **Type of depression** MDD **Intervention** ESC CIT 10 mg CIT 20 mg	**Inclusion criteria:** • Adults (age range): 23 to 45 • Diagnosed with MDD according to DSM-III or -IV: DSM-IV • MADRS: Total Score ≥ 25 • Opinion of treating psychiatrist, potential benefit from treatment with 1 or other study drugs **Exclusion criteria:** • Pregnant • Lactating • Concomitant psychotheraputic or psychotropic medications • Oral antipsychotic drugs or MAOIs w/in 2 weeks • Depot antipsychotic preparation within 6 months • SSRI, SNTR, or TCA within 1 week or FLUOX within 5 weeks • Mania or any bipolar disorder, schizophrenia,	**Groups similar at baseline** Yes **n =** D1: 109 D2: 111 D3: 110 **Mean age, years** D1: 35.19 D2: 34.79 D3: 35.12 **Sex, % female** D1: 61.1% D2: 57.5% D3: 56.5% **Race, % white** D1: 100% D2: 100% D3: 100% **Baseline HAM-A** NR **Insomnia, %** NR **Concomitant anergia, %** NR **Experienced prior depressive episodes, %** D1: 14.8%	D1: 1/106 (0.9%) D2: 1/108 (0.9%) D3: 1/109 (0.9%)	spontaneously reported

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
to adverse events, % D1: 0 D2: 0 D3: 0 **Withdrawals due to lack of efficacy, %** D1: 0 D2: 0 D3: 0 **Rate of adherence or compliance** Potentially non-compliant patients were not included. No methods were specifically employed to assess compliance. No deviations were reported. **Comments** Attrition: Seven participants withdrew consent and one patient withdrew due to recurrence of a pre-existing condition. **Study Quality:** Fair		or any psychotic disorder, or display of any psychotic features, • OCD, mental retardation or any pervasive developmental disorder, • Eating disorder (anorexia nervosa or bulimia nervosa), or dementia • Alcohol or drug abuse within previous 12 months • Other serious illnesses or sequela of serious illness • ESC or CIT usage within 60 days • Severe drug allergies or hypersensitivity • Inability to comply with protocol • Undergoing treatment with antiparkinsonian compound, barbiturate, chloral hydrate, lithium, anticonvulsant, or hypnotic and anxiolytic. **Outcome measures** • MADRS: Primary efficacy measure. A secondary efficacy measure was reported in changes from baseline in total score in a subgroup of severely depressed patients (MADRS total score ≥35)	D2: 9.4% D3: 9.3% **Comments:** MADRS total score, mean (SE) 34.78(0.34) MADRS total score, mean (SE) 35.40(0.32) MADRS total score, mean (SE)35.70 (0.37)		

Study Characteristics	Research Objective Study Design	Inclusion/Exclusion Outcome Measures	Population Characteristics	Sexual Dysfunction (SD) Outcomes/ Adverse Events	Method used to determine SD
		• Also MADRS core depressions subscale score in overall population and severely depressed subgroup. This data was not abstracted but is available, if needed. • CGI-S or CGI-I: Secondary efficacy measure. Changes from baseline to end of study.			

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Electronic Supplementary Material 2:
MMA Antidepressants Update Search November 2012

PubMed:

Search	Query	Items found
#1	Search "Antidepressive Agents, Second-Generation"[MeSH] OR "Fluoxetine"[MeSH] OR "Sertraline"[MeSH] OR "Paroxetine"[MeSH] OR "Citalopram"[MeSH] OR "Fluvoxamine"[MeSH] OR "Bupropion"[MeSH] OR "nefazodone"[Substance Name] OR "mirtazapine"[Substance Name] OR "venlafaxine"[Substance Name] OR "escitalopram"[tw] OR "duloxetine"[Substance Name] OR "Trazodone"[MeSH] OR "O-desmethylvenlafaxine"[Substance Name] OR desvenlafaxine	22636
#2	Search "Depressive Disorder"[MeSH] OR "Depressive Disorder, Major"[MeSH] OR "Dysthymic Disorder"[MeSH] OR ("depression"[tiab] AND "involutional"[tiab]) OR ("subsyndromal"[tiab] AND "depression"[tiab])	73533
#3	Search #1 AND #2	6493
#4	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double- Blind Method"[MeSH] OR "Random Allocation"[MeSH] OR "Randomized Controlled Trial"[tiab]	493623
#5	Search #3 AND #4	2262
#6	Search "longitudinal studies"[MeSH] OR "cohort studies"[MeSH] OR "case-control studies"[MeSH] OR "Comparative Study"[Publication Type] OR observational stud*	2668167
#7	Search #3 AND #6	2147
#8	Search ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR ("review"[Publication Type] AND "systematic"[tiab]) OR ("systematic review"[All Fields])	51758
#9	Search #3 AND #8	51
#10	Search "Quality of Life"[MeSH] OR "Hospitalization"[MeSH]	239688
#11	Search #3 AND #10	278
#12	Search adverse event* OR "drug hypersensitivity"[MeSH] OR "drug toxicity"[MeSH] OR “hyponatremia”[MeSH] OR “seizures”[MeSH] OR “suicide”[MeSH] OR "weight gain"[MeSH] OR "Gastroesophageal Reflux"[Mesh] OR “libido”[MeSH] OR “hepatoxicity”[tw]	242140
#13	Search #3 AND #12	1157
#14	Search "drug interactions"[MeSH]	132643
#15	Search #3 AND #14	363
#16	Search "Recurrence"[MeSH] OR "remission"[tiab] OR "relapse"[tiab]	260235
#17	Search #3 AND #16	1132
#18	Search #5 OR #7 OR #9 OR #11 OR #13 OR #15 OR #17	4252
#19	Search #5 OR #7 OR #9 OR #11 OR #13 OR #15 OR #17 Filters: Humans	4207
#20	Search "Adult"[Mesh]	5095432
#21	Search #19 AND #20	3239
#24	Search #19 AND #20 Filters: Case Reports; Letter; Editorial	546
#25	Search #21 NOT #24	2693
#28	Search (#25) AND ("2011/06/01"[Date - Entrez] : "3000"[Date - Entrez])	127

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Cochrane:

ID	Search	Hits
#1	MeSH descriptor: [Antidepressive Agents, Second-Generation] explode all trees	1118
#2	MeSH descriptor: [Fluoxetine] explode all trees	1114
#3	MeSH descriptor: [Sertraline] explode all trees	562
#4	MeSH descriptor: [Paroxetine] explode all trees	721
#5	MeSH descriptor: [Citalopram] explode all trees	660
#6	MeSH descriptor: [Fluvoxamine] explode all trees	348
#7	MeSH descriptor: [Bupropion] explode all trees	435
#8	Nefazodone	259
#9	Mirtazapine	492
#10	Venlafaxine	1037
#11	Escitalopram	494
#12	Duloxetine	423
#13	Trazodone	453
#14	Desvenlafaxine or O-Desmethylvenlafaxine	55
#15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14	5823
#16	MeSH descriptor: [Depressive Disorder] explode all trees	6572
#17	MeSH descriptor: [Dysthymic Disorder] explode all trees	127
#18	(depression and involutional) or (subsyndromal and depression)	117
#19	#16 or #17 or #18	6654
#20	#15 and #19 from 2011 to 2012	104

EMBASE:

No.	Query	Results
#1	'fluoxetine'/exp OR fluoxetine OR 'sertraline'/exp OR sertraline OR 'paroxetine'/exp OR paroxetine OR 'citalopram'/exp OR citalopram OR 'fluvoxamine'/exp OR fluvoxamine OR 'bupropion'/exp OR bupropion OR 'nefazodone'/exp OR nefazodone OR 'mirtazapine'/exp OR mirtazapine OR 'venlafaxine'/exp OR venlafaxine OR 'escitalopram'/exp OR escitalopram OR 'duloxetine'/exp OR duloxetine OR 'trazodone'/exp OR trazodone OR 'desvenlafaxine'/exp OR desvenlafaxine OR 'o desmethylvenlafaxine'/exp OR 'o desmethylvenlafaxine' AND [2011-2013]/py	9,993
#2	'depression'/exp OR 'dysthymia'/exp OR 'involutional depression'/exp	284,485
#3	#1 AND #2	4,311
#4	#3 AND (2011:py OR 2012:py OR 2013:py)	4,311
#5	#3 AND (2011:py OR 2012:py OR 2013:py) AND ('clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'drug dose comparison'/de OR 'evidence based medicine'/de OR 'evidence based practice'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)	1,467
#6	#3 AND (2011:py OR 2012:py OR 2013:py) AND ('clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'drug dose comparison'/de OR 'evidence based medicine'/de OR 'evidence based practice'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND 'human'/de	1,226
#7	#3 AND (2011:py OR 2012:py OR 2013:py) AND ('clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'drug dose comparison'/de OR 'evidence based medicine'/de OR 'evidence based practice'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND 'human'/de AND ('article'/it OR 'review'/it)	1,090
#8	#3 AND (2011:py OR 2012:py OR 2013:py) AND ('clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'drug dose comparison'/de OR 'evidence based medicine'/de OR 'evidence based practice'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND 'human'/de AND ('article'/it OR 'review'/it) AND ('depression'/de OR 'major depression'/de)	1,018
#9	#3 AND (2011:py OR 2012:py OR 2013:py) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND 'human'/de AND ('article'/it OR 'review'/it) AND ('depression'/de OR 'major depression'/de)	456

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IPA & PscyINFO:

#	Query	Limiters/Expanders	Last Run Via	Results
S4	S1 and S2	Limiters - Published Date from: 20110801-20121231; Language: English; Articles about Human Studies; Publication Year from: 2011-2012; Publication Type: All Journals; English; Language: English; Age Groups: Adulthood (18 yrs & older); Population Group: Human; Document Type: Journal Article; Exclude Dissertations Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts;PsycINFO	166
S3	S1 and S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts;PsycINFO	5855
S2	DE "Major Depression"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts;PsycINFO	77499
S1	Fluoxetine OR Sertraline OR Paroxetine OR Citalopram OR Fluvoxamine OR Bupropion OR Nefazodone OR Mirtazapine OR Venlafaxine OR Escitalopram OR Duloxetine OR Trazodone OR Desvenlafaxine OR O-Desmethylvenlafaxine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts;PsycINFO	19835